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Section of Pædiatrics

President—Professor A. G. Watkins, M.D., F.R.C.P.

[*March* 28, 1952]

DISCUSSION ON THE FATE OF THE TUBERCULOUS PRIMARY COMPLEX

Dr. **Brian C. Thompson** (Physician, Windsor Chest Clinic; formerly Physician, Middlesex County Chest Clinic, Ealing): At the Ealing Chest Clinic, children below the age of 14 who attended for the first time during the years 1942–5 numbered 1,549. Three-quarters of these came for routine examination as contacts of known cases of tuberculosis, the remainder because of symptoms or already having been diagnosed as tuberculous elsewhere. Tuberculin test by Vollmer patch and, if negative, by intradermal P.P.D., was a routine procedure, though not completely achieved in every case. Positive reactors and all children with symptoms had a chest X-ray. Negative reactors continuing to be exposed to infection were retested at three-monthly intervals.

Table I.—Tuberculin Sensitivity in 1,549 Children

Examined because of contact only	1,123
Examined because of symptoms	426
Total	1,549
Tuberculin-positive on first examination	604*
Converted from negative to positive, 1942–5	51

*Including 18 not tuberculin tested but with X-ray evidence of calcified lesions in the chest.

The manifest tuberculous lesions found either at first examination or at the time of tuberculin conversion during 1942–5, which would reasonably be regarded as part of a primary infection, are shown in Table II. In addition to the lesions shown in this table, there were 7 cases of erythema nodosum and 5 of phlyctenular kerato-conjunctivitis.

Table II.—Manifest Tuberculosis, 1942–5

Intrathoracic		*Extrathoracic*	
Primary complex, active	57	Cervical lymph nodes	18
with segmental collapse	28*	Bones and joints	7
with pleural effusion	15†	Abdomen	1
	100		
Pulmonary tuberculosis (adult type)	4		

*1 combined with tuberculous hip. †1 combined with abdominal tuberculosis.

The primary complex, whose fate is now under consideration, must be represented by the 100 cases of active intrathoracic lesions. We cannot omit, however, the much greater number of cases where the primary complex can be presumed, even if it was not radiologically visible; that is, all those children who were found to be tuberculin-positive without other evidence of tuberculosis.

Treatment.—It was our practice to admit to hospital only children who were clinically ill or those with manifest disease who could not be well cared for at home. Some of the children who were advised to go into hospital refused to go or, having gone, refused to stay. Institutional treatment did not affect statistically the prognosis.

Mortality.—Of the whole group, 12 died during the 1942–5 observation period and none since. The cause of these deaths and the groups in which they occurred are shown in Table III.

Table III.—Mortality

	Meningitis	Acute infection	Accidental	Pulm. tub.
100 cases active primary complex	2		1	
456 T.T. positive, no manifest lesion	2			
945 not T.T. positive	3	3		
4 pulmonary tuberculosis				1
	7	3	1	1

Of the 7 deaths from tuberculous meningitis, only 2 followed a manifest primary lesion and in 1 of these the child was moribund when first seen and therefore scarcely admissible. The other 5 of these deaths were unpredictable and in the circumstances at that time unpreventable. BCG inoculation might have saved the 3 who were initially tuberculin-negative. 2 of these 7 children were 3 years of

age, the others were all aged less than 1 year, as were the other 3 children who died from acute non-tuberculous infantile infections.

After-history.—Assessment of the 1,537 survivors in December 1950 showed that in those known to have been tuberculin-positive in 1942–5, no further dissemination of disease had occurred. A number of children, formerly tuberculin-negative, had become converted to positive and of these, 10 manifested gross primary lesions. In 3 other converting children, bone and joint tuberculosis developed, and in 1 tuberculosis of cervical lymph nodes. These extrathoracic lesions in every case became evident soon after conversion, always within a year. This confirms the belief that dissemination from the primary complex is an early phenomenon.

Of the 97 surviving children who originally had a manifest primary complex: 1 became subject to asthmatic attacks but has been free for the past four years. 1 developed transient phlyctenulosis. 1 developed a tuberculous neck gland. 1 child with pleural effusion developed a non-progressive apical pulmonary lesion.

Present condition of survivors.—As shown in Table IV, nearly half the children have now reached puberty and many are grown up.

TABLE IV.—AGE DISTRIBUTION OF 1,537 SURVIVORS OUT OF 1,549 TOTAL

	0–4	5–9	10–14	15–19	20–21	Total
All children seen in 1942–5	469	637	431	—	—	1,537
Age in December 1950	—	324	626	506	81	
Tuberculin-positive 1942–5	186	298	163	—	—	647
Age in December 1950	—	115	280	228	24	
Active primary complex 1942–5	27	49	21	—	—	97
Age in December 1950	—	15	47	33	2	
Age when P.T. diagnosed	—	—	2	6	—	8

The 97 children, in whom an active primary complex was originally manifest, are well and free from symptoms. X-ray shows residual calcification in 25 cases, fibrosis in 8 cases and in 3 further cases there is also a suggestion of localized bronchiectasis.

Adult-type pulmonary tuberculosis has developed in 8 cases, additional to the 4 diagnosed initially (Table II) and the 1 post-pleuritic case. None of these originally had a manifest primary complex. All were contact cases and continued in contact with an infective source up to the development of their pulmonary disease. All except 2 were girls and, as shown in Table IV, the disease appeared in the years of puberty and adolescence.

CONCLUSION

The tuberculous primary complex in children of this particular population group is usually benign and heals without any serious local residuum. Hæmatogenous dissemination very occasionally ensues. When this affects the central nervous system, it appears clinically within three or four months of the development of tuberculin sensitivity; when it affects the skeletal system, within nine or twelve months. No case of disseminated disease was seen later than this. Pleurisy with effusion occurs at about six months and is due probably to direct extension of the complex to the pleural surface (Thompson, 1949, *Brit. med. J.*, ii, 841).

The behaviour of the primary complex seems to be unrelated to its size. Meningitis ensued more often than not in children who were infected without X-ray evidence of a primary lesion. Nor is it related to intimacy of contact with an infectious source; the source was more often not to be found within the home, both in Ealing (Thompson, 1947, *Arch. Dis. Child.*, **22,** 1) and New Zealand (Thompson, 1948, *N.Z. med. J.*, **47,** 229). This suggests that the size of the infecting dose may not be a factor either. And though, in general, the younger the child the greater the probability of hæmatogenous spread, recovery usually occurred, even in infants less than 1 year of age.

Continuation of contact with an infectious source after primary infection had occurred, which was often unavoidable, did not seem to affect the subsequent course of that infection. If maintained through adolescence, however, such contact appeared to favour the development of adult-type pulmonary tuberculosis.

Deaths from tuberculosis in Ealing children as a whole, as in New Zealand children over the same period, occurred three times out of four in families unknown to the Tuberculosis Service. They numbered only 2 per annum per 100,000 total population, a figure which should become even smaller with earlier diagnosis in the meningitic stage and modern chemotherapy, and with BCG inoculation of children specially exposed to infection. It is not likely to be substantially reduced by the indiscriminate use of BCG in children of highly resistant, relatively prosperous population groups, or by efforts to detect more cases in the stage of primary infection. The latter procedure, however, may be of value in leading to detection of infectious adults.

The solution to the problem of childhood tuberculosis lies in the effective control of the disease in adults.

Mr. **Dillwyn Thomas:** Primary thoracic tuberculosis occurring in childhood, unless complicated by hæmatogenous dissemination and meningitis, is stated by the majority of workers to pursue a benign course. Nevertheless, it appears from material studied, which I now present as an opener of this discussion, that some patients do give rise to anxiety, and the opinion has been formed that they cannot be regarded as suffering from a benign disease.

The children forming this group had not responded to conservative therapy of prolonged bed-rest and antibiotics, and were submitted for surgical opinion.

Thoracotomy was performed in 37 cases.

The indications for such an active policy were: (1) Stridor with cyanotic attacks. (2) Progressive enlargement of mediastinal glands in spite of conservative treatment. (3) Gross distortion of the bronchial tree and bronchiectasis. (4) Obstructive emphysema. (5) Lack of resolution, or progression of the pulmonary shadow in spite of conservative treatment, particularly when accompanied by T.B.-positive gastric contents.

Almost all the cases had received at least one course of streptomycin and PAS prior to admission to Sully Hospital.

The major difficulty in pre-operative assessment was the interpretation of the X-ray film. A particular shadow was variously described as atelectasis, epituberculosis, tuberculous pneumonia or obstructive pneumonitis, according to the views of the observer. In 3 of the cases, what appeared on X-ray to be a pulmonary shadow, was found on thoracotomy to be a large glandular mass eroding the adjacent portion of lung.

Another difficulty was the decision to operate because of a worsening X-ray in the absence of any marked deterioration in the patient's general condition.

Operation.—The thoracotomy was considered as an exploratory measure, the full nature of the operation being determined by the findings on exploration.

Glands.—It was not always possible to enucleate the glands. Many of the larger masses were found to be closely adherent to vessels, making enucleation hazardous. Under such conditions the gland mass was incised, and the caseous and purulent material evacuated. The abscess cavity was then cleaned and, unless the gland had eroded the bronchus, no effort was made to close off the abscess cavity from the pleura. When the gland had already eroded the bronchus and a fistula existed at the base of the abscess cavity, the gland capsule was sometimes used to repair the fistula. The suture material was nylon. In other cases a pleural graft was used for the same purpose.

If the affected segment of lobe was found to be the site of caseous tuberculosis it was removed at the same operation. In one case to be described the diseased lobes were removed at a subsequent operation.

It is obvious that when glands are incised and the abscess evacuated, the pleura is almost certain to be soiled with tuberculous pus. No established pleural infection resulted, because the pleural space was rapidly obliterated by using continuous negative suction via the drainage tubes in the post-operative period. It was found that water-suction was very effective when there was a larger air leak from the alveoli or an imperfectly repaired bronchial fistula.

During the immediate post-operative period the children were nursed on the contralateral side over an arched plaster case—making the chest wall on the uppermost convex. This has proved a useful measure in preventing post-operative atelectasis, which did not occur in this series.

The rapid obliteration of the pleural space and the prevention of atelectasis have been responsible for the absence of complications.

ANALYSIS OF CASES SUBMITTED TO THORACOTOMY

Hilar adenectomy only	10 cases	
Removal of lobe, or segment, + glands ..	27 cases	Mortality (due to hæmorrhage at operation) 1
Total	37 cases	

Pathology of specimens removed at operation.—The segments and lobes removed at operation have, with the exception of one doubtful case, showed areas of caseous tuberculosis, some extensive.

In the cases showing gross tuberculosis, a gland has been found perforating into the draining bronchi.

The doubtful case has been reported as an epithelioid reaction involving almost the whole of the left upper lobe. No caseation was demonstrated.

ILLUSTRATIVE CASES

Case I.—C. H., aged 2 years 11 months. Admitted to Llandough Hospital 13.11.50 because of lassitude; general condition fairly good. X-ray (Fig. 1) "Described at the time as atelectasis". Soon after admission the child developed stridor, with attacks of cyanosis, which became progressively worse. Mantoux positive.

He was admitted to Sully two months later with gross stridor and attacks of cyanosis.

Bronchoscopy revealed stenosis by pressure on the trachea, proximal to the carina; no gland seen.

Gastric contents negative for tubercle bacilli.

6.2.51: Right thoracotomy and resection of the upper and middle lobes. The upper lobe was solid and there

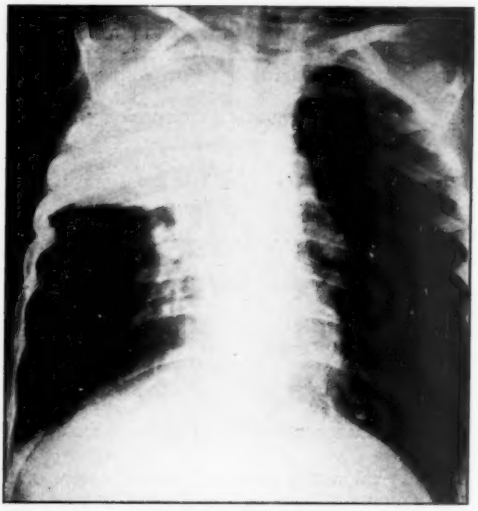

FIG. 1 (*Case I*, C. H.).—Total opacity of the right upper lobe. "Described at the time as atelectasis."

FIG. 2 (*Case II*, L. S.).—Lateral X-ray demonstrating gross middle lobe consolidation.

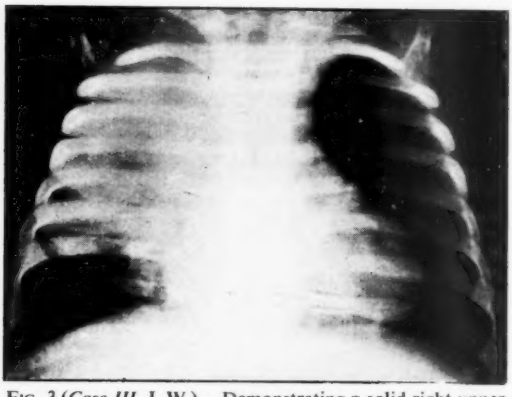

FIG. 3 (*Case III*, J. W.).—Demonstrating a solid right upper lobe with a suspicion of a cavity.

were numerous glands at the hilum. The trachea was perforated during evacuation of a large paratracheal gland, and repaired with a pleural graft.

Pathology.—Upper lobe solid, with areas of caseous tuberculosis.

An example of operation performed for severe stridor and attacks of cyanosis.

Case II.—L. S., aged 5 years 6 months. Admitted to Llandough Hospital in September 1950, with right-sided pleurisy, but prior to this was considered by her parents to be unwell.

X-ray (Fig. 2) showed middle lobe consolidation. The bronchoscopy and bronchograms were normal. Mantoux test positive.

13.3.51: Thoracotomy—the middle lobe was removed, and also a caseous lymph gland perforating the middle-lobe bronchus.

Pathology.—The middle lobe was completely solid with caseous tuberculosis.

Case III.—J. W. Date of birth 29.7.50. History of cough and weight loss at 5 months.

X-ray (Fig. 3): Solid right upper lobe with suspicion of excavation. Mantoux test positive. Laryngeal swab positive for tubercle bacilli. Admitted to Sully at the age of $7\frac{1}{4}$ months. There was no change, clinically or radiologically, in spite of a course of streptomycin and PAS. The prognosis was poor because of the child's age.

17.4.51: The right upper lobe, and numerous large caseating glands, were removed. Post-operative course was uneventful.

Pathology.—Caseous tuberculosis of the right upper lobe with a circular cavity the size of a penny, full of caseous material.

Case IV.—J. D., aged 7 years. History of cough for three years, and more recently of febrile attacks. Mantoux test positive.

March 1951—X-ray (Fig. 4): Appearance diagnosed as primary tuberculosis.

January 1952—X-ray (Fig. 5): Appearance of right middle and lower lobe atelectasis, with a large hilar shadow.

The child was now slightly cyanosed.

Bronchoscopy (Morriston Hospital).—"Complete obstruction of lower part of the right main bronchus by external pressure and some suggestion of erosion of mucous membrane. The left main bronchus lumen

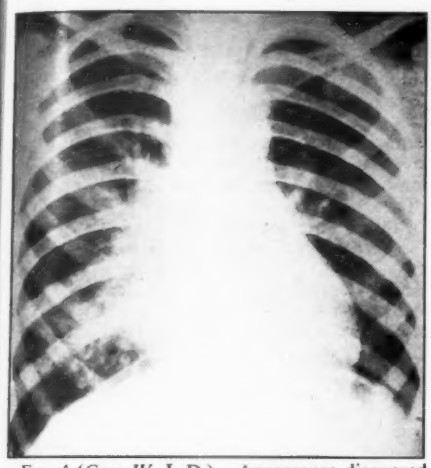

FIG. 4 (*Case IV*, J. D.).—Appearance diagnosed as primary tuberculosis in March 1951, showing enlarged hilar glands and infiltration in the right lower lobe, and some suggestion of obstructive emphysema.

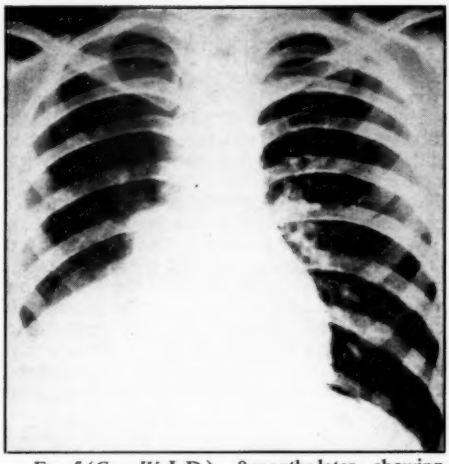

FIG. 5 (*Case IV*, J. D.).—9 months later—showing enlarged hilar shadow and atelectasis of the middle and lower lobes.

considerably narrowed by gland ulcerating through the mucosa immediately distal to the carina on the medial side."

The child was admitted to Sully in February 1952.

5.3.52: Right thoracotomy—A large mass of caseous material was removed from the region of the carina. At the end of the operation perforations were observed in both the right and left main bronchi. The left one was only partially repaired, and an air leak was present at the end of the operation. This was controlled with high negative suction by means of a water-suction pump; the lung re-expanded satisfactorily. It was decided at this operation that, owing to a degree of anoxia that existed during the repair of the perforations, removal of the solid lobes should be delayed.

25.4.52: Right middle and lower lobes removed. Post-operative course uneventful.

23.6.52: Bronchoscopy showed a slight degree of roughening only, present on the medial aspect of the left main bronchus.

Pathology.—Bronchiectasis of the middle and lower lobes, with multiple areas of caseous tuberculosis.

SUMMARY

Cases of primary tuberculosis giving rise to anxiety have been submitted to thoracotomy with enucleation or evacuation of the hilar glands in 10 cases.

27 cases had a lobe or segment removed together with glands.

One case was lost because of hæmorrhage at operation. The indications for the active procedure have been given, and the pathological findings stated.

ACKNOWLEDGMENTS

I would like to thank Professor Watkins, and Drs. J. Jacobs, P. Bray and R. T. Jenkins, who have referred these cases for surgical opinion and treatment. Without their interest this contribution would not have been possible.

Dr. John Lorber drew attention to the great difficulty of obtaining a truly representative sample of children with primary tuberculosis as was demonstrated by the extreme views of the two speakers. A representative sample should include all those examined as contacts, most of whom were free of symptoms. It should include those who were referred to hospital because of an illness and those in whom tuberculosis was first detected only when meningitis or miliary tuberculosis was already present. Dr. Lorber had studied such a large and representative sample for several years. Special attention was paid to a homogeneous age-group of infants under 2 years of age. He agreed with Dr. B. C. Thompson that even in this most vulnerable age-group the immediate prognosis was good in most of those who were diagnosed before complications developed, and the majority went through their illness without symptoms. Nevertheless, there was an approximate 10 per cent incidence of meningitis occurring within the first eighteen months of detection of tuberculosis and a rather smaller incidence of disseminated or localized forms of hæmatogenous tuberculosis. It appeared, therefore, that Dr. Thompson's figures were too optimistic and might be due to bias by a heavy preponderance of contact

cases and failure to trace all his patients for follow-up studies. Further, a much longer period of observation was necessary to assess the delayed effects of primary tuberculosis in childhood. As Lincoln (1950) and Myers (1951) have proved, persons known to have had primary tuberculosis in childhood develop pulmonary tuberculosis in a much higher percentage than a comparable sample from the general population who were known not to have had primary tuberculosis in childhood.

He could not agree with Dr. Thompson that most cases of tuberculous meningitis occurred in non-tuberculous families or where the contact was not known. In a survey of the contact history of 150 children with tuberculous meningitis (Lorber, 1950) he found that in four-fifths the infecting adults were either known cases of tuberculosis or else their symptoms were such that they should have been diagnosed before their children developed meningitis. These figures show the great responsibility of chest physicians in the prevention and early diagnosis of tuberculous meningitis.

With continued observation he was able to detect the earliest signs of meningitis in infants with primary tuberculosis, and treat them so that in the course of three years there was only a single death from tuberculosis in a group of some 100 infants. No death occurred from the lung lesions, although no specific treatment was given for primary tuberculosis and most children were not admitted to hospital for this. Many extensive lesions, like those shown by Mr. Dillwyn Thomas, have eventually cleared up and the patients are symptomless. This did not mean that surgery might not play an important part in the treatment of selected cases, but before advising thoracotomy one would have to know the mortality rate of the operation, and the post-operative complications and morbidity.

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Dr. Ronald MacKeith hoped that tuberculosis would be eradicated in this country in the next ten years; but he thought that even so during this time surgery would have a part in dealing with certain difficult sequels of primary infection.

Dr. Harley Stevens said that in former days gross abnormalities, similar to those shown by Mr. Dillwyn Thomas, had seemed to resolve eventually leaving a contracted bronchiectatic lobe or calcified masses in glands and lung substance.

More recently the routine practice of guinea-pig inoculation of stomach contents at Peppard Sanatorium had shown that a high proportion of these primary conditions associated with caseous glands and segmental collapse continued to produce tubercle bacilli over a long period. They should be regarded as potential sources of infection, either in the home, where there were other children, or at school if in that age-group. Children did cough quite violently at times, even if they did not produce a measurable quantity of sputum. For that reason the group should be segregated in special residential institutions until they became non-infectious—and this was costly.

The occasional case had such gross involvement of glands and lung that surgical exploration had seemed justifiable after an interval of two years. He thought that the period of expectant treatment might now be no more than eighteen months in some cases, but he did not wish to see it further reduced.

Dr. J. J. Kempton said that surgery could do a great deal for many of these cases. At the present time the positive tuberculin test was perhaps the greatest cause of unnecessary invalidism in childhood. They all knew the mother who, when told that the test was negative said "Thank God" in the tone of one who has narrowly escaped being burnt alive.

The problem was what to say to the parents of the child who was tuberculin positive, with no referable symptoms and minimal radiological signs. He usually said (rather than embark on a detailed explanation which would not be understood) that the test did not mean that the child had tuberculosis, but that he might get it, and that he should be watched on account of this possibility.

Dr. J. Jacobs said that as the pædiatrician associated with the work he would like to explain the one death in the series. It should be made clear that in this case the tuberculous lesion had actually involved the pulmonary artery which had fallen to pieces during operation. The case was one of so-called "epi-tuberculosis", a term to be deprecated and really no longer to be used, for, despite the name, at autopsy caseous lesions were found throughout the segment and miliary lesions in liver and spleen. One found it very hard to accept that the future of these large caseating lesions was benign, and one wondered how frequently—prior to becoming one of Brock's middle lobe syndromes—these lesions actually were a source of infection to other people. The lesions, especially the hilar nodes, were very difficult to assess, for in ordinary radiography they occupied one of the relatively "silent areas" of the X-ray.

With regard to gastric lavages, many of the children had positive results, one in particular had a positive result on the day before operation, all previous lavages having been negative.

Section of Anæsthetics

President—JOHN GILLIES, C.V.O., M.C., M.R.C.P.Ed., F.R.C.S.Ed., F.F.A. R.C.S.

April 4, 1952]

Asphyxia and the Electrolytic Balance [*Abstract*]

By Professor R. J. S. McDOWALL, F.R.C.P.Ed.

King's College, London

ASPHYXIA is caused by the accumulation of carbon dioxide in the body, together with oxygen lack. It may affect a part of the body or the whole. The latter is the more important to anæsthetists and is most commonly produced by anything that interferes with the aeration of the blood in the lungs. Provided that the asphyxia is not produced by injury or depression of the central nervous system, such as may occur in too deep anæsthesia, respiration is stimulated by the carbon dioxide acting directly on the medulla, and by oxygen lack and carbon dioxide acting on the carotid and aortic bodies. The latter are also stimulated by lack of oxygen, which, however, is otherwise a general, and very serious, nervous depressant. This we see dramatically in the unconsciousness which is produced by breathing any gas, other than oxygen, for a few minutes.

The effect on the circulation is mixed, that is to say, there is a central stimulation of the sympathetic and of the vasomotor centre in particular, but, as metabolites accumulate peripherally, the capillaries dilate, and, in a few minutes, lack of oxygen causes the heart to fail. There is, therefore, at first a rise of arterial pressure, due to increased cardiac output and peripheral resistance, followed by a fall. The venous pressure rises at first, owing to the generalized vasoconstriction, and continues to rise still further as the heart fails. A characteristic of the final failure is slowing of the heart due to increased action of the vagi. Hæmorrhage, and anything which depresses the circulation materially, produce essentially similar effects on the tissues as a whole.

Now, in asphyxia, the really important thing is the lack of oxygen; this cannot be over-emphasized. The extent to which the body can adapt itself to high alveolar carbon dioxide, especially if it is brought about slowly, is quite remarkable. The harmful effect of lack of oxygen, on the other hand, is cumulative. As J. S. Haldane often remarked, "oxygen lack not only stops but wrecks the machine". After severe anoxia recovery is slow, and may never become complete. This has been shown to be specially true of the cerebral cortex, rendered anoxic by occlusion of the cerebral arteries, but all tissues are affected to a lesser extent, depending on the duration of the anoxia.

Within recent months, my colleagues, M. Z. Awad, A. F. Zayat, and I, have shed some light on how anoxia produces its deleterious effects. It has been found that the anoxia completely upsets the electrolytic balance between the inside and outside of cells—upon which their excitability appears to depend.

Perhaps I should explain this to those who are not familiar with such matters: It has been found that the sodium chloride in cells generally is not, as used to be thought, in equilibrium with that of the tissue fluid in which they are bathed. Cells contain very much less sodium chloride than tissue fluid or blood plasma. Individual cells differ, but the proportion may be as little as one to ten, and it is now believed that there exists a mechanism—conveniently known as the sodium pump—which prevents the entrance of sodium into the cells. If, for example, we place isolated diaphragm of the rat in Krebs' solution (a modification of Ringer's solution), and deprive it of oxygen, a neuromuscular block like that caused by curare occurs, and later the muscle itself fails. Provided the anoxia has not been allowed to persist too long, complete recovery of the block or of the muscle can be brought

about by reducing the sodium chloride in the external solution by about a quarter (0·69% to 0·48%). Changes in the other ions in the solution or in the osmotic pressure are without effect. The explanation of this somewhat dramatic finding appears to be that the concentrations in and out of the cell tend to equalize when the cell membrane is made more permeable by the anoxia. The sodium chloride enters the cells. It is important to emphasize that when the anoxia has been quite short (three minutes) the effect and the delayed depression are not prevented by the readmission of oxygen. If, however, the concentration of the sodium chloride outside the cell is reduced, the gradient against which the "sodium pump" has to work is made easier, and the normal ionic relations and excitability return. The membrane does not recover, for the tissue is now depressed by even normal sodium chloride. This effect of anoxia appears to be a general phenomenon, probably affecting all tissues. The unexpected and new feature of one investigation has been the demonstration of the slow, insidious and delayed effect of the anoxia—even in the presence of oxygen. We have demonstrated it on nerve and on striped and cardiac muscle, all of which are most profoundly depressed. We have been able to show that the effect of reduced external solution is more beneficial in restoring the responses of cardiac muscle, previously anoxic, than the best cardiac tonic. It is possible, therefore, that some of the great benefit which accrues from reduction of the sodium intake, in some cases of cardiac disease, may be due to such a direct action on the cardiac muscle.

It must be emphasized that the results which have been described here have, so far, been obtained only on isolated tissues. We have still a long way to go, but they point the way and show how the problem may be studied. At present, we are trying to discover means of applying these new basic facts to the intact body and we hope to devise means by which the deterioration, and often fatal delayed effects of oxygen lack, may be prevented.

[*May* 2, 1952]

Caudal Analgesia—Clinical Applications in Vasospastic Diseases of the Legs and in Diabetic Neuropathy [*Abridged*]

By A. H. Galley, M.B., B.S., F.F.A. R.C.S.

When a local analgesic solution is injected into the caudal canal it forces its way upwards to a varying distance between the theca and the bony spinal canal into an annular space known as the epidural, peridural or extradural space. As the fluid rises in this space it overflows through the vertebral foramina to produce a multiple paravertebral block, the height of analgesia being proportional to the volume of fluid injected. Evidence that there is continuity between the extradural space and the paravertebral spaces is now overwhelming and has been demonstrated in various ways:

(*a*) By injecting 2% procaine in Lipiodol into the extradural space at various levels and taking serial X-ray photographs (Odom, 1940). Fluid was seen to flow into the paravertebral spaces via the vertebral foramina.

(*b*) By injecting methylene-blue solution into the caudal canal of a cadaver and subsequent dissection (Hingson and Edwards, 1942; Macintosh and Mushin, 1947). The caudal canal, the extradural space to the level of the foramen magnum, the vertebral foramina and all the paravertebral spaces were stained with the dye. This method also demonstrated that while the paravertebral spaces were not in direct communication one with another, they did intercommunicate via the extradural space.

(*c*) Fluids injected into the thoracic and lumbar regions of the extradural spaces will issue through needles correctly placed in adjacent paravertebral spaces (Macintosh and Mushin, 1947).

(*d*) Odom (1937) demonstrated that a negative pressure exists in the cervical, thoracic and lumbar regions of the extradural space, decreasing towards the lumbar region and disappearing in the caudal canal. Recently Haxton (1949) discovered that a negative pressure could often be shown to exist in the paravertebral spaces although he failed to grasp the fact that this was probably communicated from the extradural space.

A multiple paravertebral block instituted by means of caudal analgesia will anæsthetize the following structures: the anterior and posterior spinal nerve roots and the posterior root ganglion ensheathed in a tube of tissue which is a prolongation of thecal fibres; the common spinal nerves in the spinal foramina; the sympathetic ganglia of the paravertebral chain, the white and grey rami, visceral sensory nerves and the common spinal nerves in the paravertebral spaces. The viscerosensory afferents accompany sympathetic filaments but pass through the sympathetic ganglia without synapsis and travel onwards to their cells of origin in the posterior root ganglion. Somatic sensory nerves (afferents) arrive in the paravertebral space in the common spinal nerve together with motor nerves and other afferents subserving the sensations of touch, pressure, cold, heat and position sense (kinæsthetic or proprioceptor afferents).

Differential Anæsthesia

When a mixed nerve is bathed in a local analgesic solution the sensory nerves are anæsthetized more easily than the motor nerves; in fact a solution of 0·2% procaine injected into the subarachnoid space as a drip can be arranged to anæsthetize only sensory nerves leaving motor nerves unaffected. Even during clinical spinal analgesia sensory paralysis is predominant and a sense of touch usually remains together with some motor power although the latter is greatly diminished. The reason for this discrepancy appears to be due to the difference in size of the various fibres concerned as is shown in Table I. This discrepancy between sensory and motor paralysis is known as "differential anæsthesia". It is more marked in extradural block than in spinal analgesia for the following reasons: Within the subarachnoid space the fibres of both roots fan out and can be easily affected by solutions of analgesic drugs dissolved in cerebrospinal fluid (Galley, 1950). In the extradural or paravertebral spaces the nerve fibres are bundled together and covered in sheaths of varying thickness and are, therefore, less accessible and are blocked with greater difficulty. Thus any discrepancy is exaggerated.

Relationship Between Diameter of Nerves and Their Function

Gasser and Erlanger (1936) have divided nerve fibres into three categories: "A", "B" and "C". Such knowledge as we have about these three groups is epitomised in Table I.

TABLE I.—THE EFFECTS OF SPINAL OR EXTRADURAL ANALGESIA UPON THE THREE TYPES OF MAMMALIAN NERVE FIBRES

(A. H. Galley, 1950)

Type of fibre	Function	Effect of blocking spinal nerve or nerve roots
	(*a*) Skeletal *motor* fibres	(*a*) Muscle paralysis (risk of respiratory failure)
"A" FIBRES Large Myelinated (1 to 20μ)	(*b*) Fibres from *touch* endings	(*b*) Loss of touch sense
	(*c*) *Proprioceptor* fibres, e.g. from muscles, tendons, joints, ligaments and periosteum	(*c*) Loss of stretch-reflexes and muscle tone giving "muscular relaxation". Loss of joint sense, &c.
	(*d*) Small fibres subserving *pain* of a sharp or shooting nature (well localized)	(*d*) Analgesia to sharp pain (e.g. cutting) and referred shooting pains
	(*e*) Small fibres subserving *thermal* sensations	(*e*) Loss of thermal appreciation
"B" FIBRES Large Myelinated (1 to 3μ)	Most preganglionic sympathetic fibres (involuntary autonomic motor fibres) such as the *white rami*	(*a*) Vasodilatation (*b*) Loss of power of sweating (*c*) No reflex action of pilomotor muscles (*d*) Constriction of bowel and relaxation of certain sphincters (*a*)–(*d*) In the area affected (*e*) Lowering of B.P. if block includes segments above L.1
"C" FIBRES Unmyelinated, i.e. naked axon cylinders $<1\mu$	(*a*) Some pre- and all post-ganglionic sympathetic motor fibres (grey rami)	(*a*) Some sympathetic paralysis as above (grey rami unaffected by subarachnoid block)
	(*b*) Afferents mediating dull aching or burning *pain* (badly localized)	(*b*) Analgesia to "second component" of pain due to cutting or burning, deep limb pain and pain from viscera
40% of posterior nerve-root fibres are in this category	(*c*) Afferents mediating *thermal* sensations	(*c*) Loss of thermal appreciation
	(*d*) Afferents mediating sensations of *itching* and tickling (probably identical with *b*)	(*d*) Relief of skin irritations

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There are two distinct types of fibre subserving the sensation of pain (*a*) Unmedullated fibres of Group C. These convey dull aching pain which is poorly localized. (*b*) The finest of the medullated fibres of Group A which mediate pain, sharp or shooting in character and fairly well localized. By definition, all sympathetic (afferent) fibres are in Group B and have diameters approximating to the two types of fibre which convey sensations of pain. *Similar concentrations of local analgesics will, therefore, anæsthetize pain or sympathetic filaments without differentiation.*

Reaction of the Extradural Space to Injections

Local analgesics were first injected into the extradural space at the beginning of the century (Sicard, 1901; Cathelin, 1901). Odom (1940) was the first practitioner to try out solutions other than aqueous procaine. For some time he regularly used oily solutions as he thought that the analgesic drug was more easily transferred to the nerve fibres. One of these mixtures actually contained 1% ethyl ether. The lining and contents of the extradural space would appear to be unusually resistant to pharmacological insults; for Odom also reports a case of carcinoma of the pelvis in which he used 95% ethyl alcohol without untoward reaction—and, incidentally, without effecting motor paralysis. Kenny (1947) employed caudal Proctocaine for the relief of intractable pain due to carcinoma of the pelvis without untoward effect.

INJECTION TECHNIQUE

Full descriptions of the technique of caudal injection are to be found in the relevant literature (Hingson and Edwards, 1942; Galley and Peel, 1944; Galley, 1949, 1950). One or two points, however, are worthy of emphasis. Oily solutions must be warmed prior to injection or the process will be slow and tedious. Any fall of blood pressure is attributable to dilatation of the vessels of the legs; raising the legs vertically corrects the hypotension by returning blood to the general circulation—this measure is also valuable when collapse of the circulation occurs during spinal analgesia. It is advisable to warn nurses and house officers to make sure that retention of urine does not occur after analgesia has been effected. Owing, perhaps, to the large size of the fibres involved in the bladder-emptying mechanism we have not seen a case (using oily procaine solutions) where urinary retention has actually occurred. Where walking is deemed advisable patients should be exercised the day after injection of oily solutions; full muscular power returns in two or three days.

Clinical Experiments and Applications

Cold feet.—Several patients suffering from sensations of intense cold in the lower part of the legs and feet have been given single-dose caudal analgesia with varying agents, including Proctocaine, aqueous solutions of Nupercaine 1 : 1,000, and 1·5% solutions of Xylocaine. Most of these patients showed little or no rise in skin temperature during the caudal block; yet, despite this, the majority felt warmer in the deep tissues and the effects have in most cases been lasting. The probable explanation of this apparent paradox is that vasodilatation in the deep tissues may occur without a corresponding rise in the temperature of the overlying skin. That the beneficial effect should be permanent will be discussed later.

Vasospastic Disease of the Legs

In severe obliterative vascular disease of the legs caudal injections of Proctocaine have been of considerable advantage. The first case on which this form of treatment was used was an elderly man of nearly 80 years, who had gross arteriosclerosis with extensive areas of gangrene on each foot and who was suffering from continuous pain which necessitated four-hourly injections of morphia, pethidine or Physeptone, the drug being changed from day to day. Proctocaine 50 ml. injected into the caudal canal produced a cessation of pain for just over three months, a considerable improvement in the blood supply of each leg and a rapid demarcation between the good and the gangrenous skin. When, at the end of thirteen weeks, the pain returned, it was decided to amputate one leg above the knee. During the operation the surgeon remarked that the blood supply to the muscles was unusually good and expressed the wish that he had known this soon enough to have saved the knee-joint. A fortnight later the other leg was amputated below the knee and healed rapidly. Since then other cases have been treated similarly. The time during which the patients have been pain-free has varied but in each case a rapid demarcation of gangrenous areas has occurred and extra joints have been saved.

Several cases of severe intermittent claudication have been submitted to extradural Proctocaine, some suffering from diabetes mellitus and others solely from obliterative arterial disease. For varying times after injection all these cases have shown a marked symptomatic improvement; pain on walking either no longer occurred or the walking distance prior to the onset of pain was greatly increased. Other improvements observed were a cessation of the feeling of coldness of the feet and an ability to cross the legs while sitting without bringing on cramp in the calf muscle. In one case the effect has been permanent but most patients experienced some deterioration after the original improvement. All, however, were much better off than before the injection. A similar experience has been reported following multiple paravertebral injections of Proctocaine (Wilson, 1948).

Phlegmasia Alba Dolens

If taken early, the white-leg of pregnancy or of the puerperium readily responds to all forms of sympathetic block, including caudal analgesia (Hingson, 1947, 1949; Steel, 1948). The combination of pathological, physiological and hydrodynamic mechanisms involved is as follows: First of all the femoral or other deep vein becomes thrombosed. This insult initiates a simple spinal reflex producing spasm of the homolateral small veins and arterioles, particularly the latter. The blood stream is then brought almost to a standstill which, in turn, leads to a fall in the temperature of the leg and to hypoxia of the tissues. Hypoxia in the cells of the capillary walls causes permeability of these vessels, the fluid contents of the blood escape into the tissues and œdema ensues. As the œdema progresses the lymphatics, which are now almost the only means of carrying off fluid from the leg, are subjected

to increasing pressure. A vicious circle thus comes into play and it is imperative to perform a sympathetic block at an appropriate level before œdema-pressure makes it impossible to increase the venous and lymphatic return from the leg. With aqueous solutions it is often necessary to perform caudal analgesia for some hours and, perhaps, to repeat this in a day or two lest the spasm returns. Table II shows how such a case was caught in time and was satisfactorily healed by caudal injections of Proctocaine. It was an unusual case in that the "white-leg" commenced a day or two before delivery instead of afterwards, as is more common.

TABLE II.—CAUDAL PROCTOCAINE FOR PHLEGMASIA ALBA DOLENS

Time	(hours)	Management	Diameter of thighs (inches)	
			Right	Left
First day	22.25	Caudal Metycaine 1½% 45 c.c.	28 cold	20 warm
	23.55	Caudal Proctocaine 40 c.c. Anticoagulants — Relief of pain in right leg		
Second day	10.00	Anticoagulants — No pain in right leg	26¼ warm	20 warm
	19.00		24½ warm	20 warm
Third day	A.M.	Went into labour	23 warm	20 warm
	14.05	Caudal Metycaine 1½%		
	16.25	Delivered	22¼ warm	20 warm
Sixth day		Anticoagulants stopped	20¾ warm	20 warm

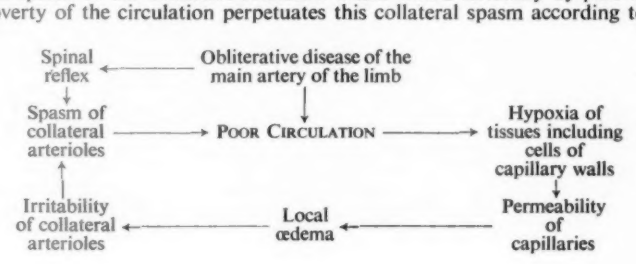
Diabetic Neuropathy

Most recent research into the causation of diabetic neuropathy (Martin, 1952) shows that there is a generalized degeneration of "C" fibres in the nerves concerned whilst the larger fibres escape destruction and retain their myelin sheaths. As degeneration of the nerves proceeds there is often sufficient pain from the affected area to make the patient miserable. When degeneration of the nerve, and of its parent cell within the dorsal root ganglion, is complete the pain ceases. In conjunction with Dr. Mencer Martin (Diabetic Research Scholar, King's College Hospital), I have treated diabetics having this disability with various forms of caudal analgesia. Using 1 : 1,500 solution of Nupercaine (ineffective when used in this strength for surgical purposes) we were always able to alleviate this form of pain without greatly diminishing sensations of pin-prick in such portions of the leg as were not already analgesic by virtue of the disease itself. The pain returned when the effect of the injection wore off. Caudal injections of Proctocaine caused the pain to disappear and the relief was permanent.

DISCUSSION

Caudal analgesia by single-dose injections of aqueous solutions blocks "B" and "C" fibres for periods of 40 to 90 minutes according to the drug used. Analgesia can be prolonged indefinitely by leaving a catheter or metal needle in the sacral canal and giving serial doses every 45 to 60 minutes according to the type of drug. Oily solutions of procaine produce blocks lasting several hours, analgesia sometimes taking twelve to twenty-four hours to wear off.

How can we explain the permanent or prolonged relief obtained by analgesia lasting at best for a day? It would be reasonable to suppose that a vicious circle of some sort is broken in each type of case. In phlegmasia alba dolens we have already seen the probable explanation of the relief of this complaint when sympathetic block is performed. Leriche (1939) postulates that, in cases of obliterative arterial disease, the poor circulation due to the diminished lumen of the main artery of the limb is aggravated by a spasm of the collateral arterioles which would normally by-pass the obstruction. Further, the poverty of the circulation perpetuates this collateral spasm according to the following schema:



The interruption of such a self-perpetuating system as the above by caudal or other type of sympathetic block would account for the relief obtained.

The permanent effect in cases of diabetic neuropathy accompanied by constant pain is not covered by this explanation, for histological sections of the nerves affected (together with surrounding tissues) show no signs of obliterative arterial disease (Martin, 1952). Nor can vasodilatation be obtained in the affected limbs by "reflex" heating, intravenous Priscol or any form of sympathetic block (Martin, 1952). It is reasonable to infer, therefore, that the pain is not ischæmic in origin. In these cases pain may, however, be due to one of two causes:

(*a*) The degenerating fibres probably discharge afferent impulses which keep the sensory neurones in the spinal cord and dorsal root ganglia under continuous bombardment. Similar bombardments are known to invoke hyperexcitability of neurone-pools which can permanently be relieved by temporary block of the fibres effecting the bombardment (Reynolds and Hutchins, 1948). Or

(*b*) A case of causalgia has been reported with a painful area of skin supplied by three cutaneous nerves which had sustained injury (Weddell *et al.*, 1947). When these nerves were fully recovered the causalgia disappeared but could temporarily be reproduced by anæsthetizing any one of the three nerves concerned. It may be that certain neurone-pools are relatively quiescent when they receive their normal pattern of afferent impulses but that distortion of the pattern sometimes causes the pool to fire off impulses which are interpreted by the sensory analysers in the thalamus or cortex as painful. It may well be that the degenerating "C" fibres of diabetic neuropathy produce such a distorted pattern and that the tumult in the relevant neurone-pool is subdued by caudal block.

Conclusion

Caudal analgesia supplies a form of multiple paravertebral block which necessitates only one injection. The injection of intermittent doses of aqueous analgesic solutions or single injections of oily solutions often break the vicious circles of pathological events associated with vasospastic disease of the leg or diabetic neuropathy.

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Section of Odontology

President—R. A. Broderick, D.S.O., M.D.S.Birm., F.D.S., M.B., Ch.B.Birm.

[*May* 26, 1952]

Meeting Held at the Royal College of Surgeons, London

Three Specimens in the Odontological Section of the Royal College of Surgeons' Museum

By Sir Frank Colyer, K.B.E., F.R.C.S.

The teeth shown in Fig. 1 were removed from the mandible of a girl aged 2 years 9 months. The child was admitted to hospital for a swelling of the right side of the mandible extending from the angle to the corner of the mouth. All the milk teeth were erupted and there was a circular opening in the gum about 1·5 cm. in diameter from which projected the geminated crowns of a second incisor and canine. At the operation the erupted deciduous molars were removed; they are shown in the top row of the illustration. Below these was a thin layer of bone covering two deciduous molars and a partly formed permanent first molar which, together with the geminated incisor and canine, are shown in the middle row. Beneath these was another layer of bone and the two deciduous teeth and partly formed permanent molar seen in the bottom row. A feature of interest about this row is that the teeth morphologically belong to the left side.

Gibbs (1913) who communicated the case states that as far as he could discover "this is the first case that has been recorded of a placental mammal with definite calcification of more than two sets of teeth, and it disposes once for all of any doubt as to the possibility of polyphyodontism in them. It also lends a certain support to the contention of those who maintain that sections through fœtal

Fig. 1.—Teeth removed from the right side of the mandible of a child. Roy. Coll. Surg. Mus. Odonto. Sect. D.164.3.

Fig. 2.—*Ovis aries* (Sheep). Mandible with an accessory jaw attached. Roy. Coll. Surg. Mus. Odonto. Sect. G.5.11.

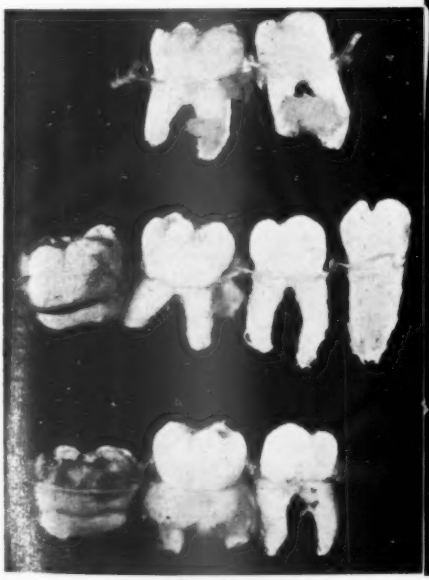

Fig. 1.

Fig. 2.

FIG. 3.—*Loxodonta africana* (African Elephant). A photograph of part of the cranium with an extra tusk in each premaxilla. Reproduced by kind permission of N. Goldstein.

FIG. 4.—*Elephas* (Elephant). A specimen showing a stage in the production of a double tusk. Roy. Coll. Surg. Mus. Odonto. Sect. G.27.9.

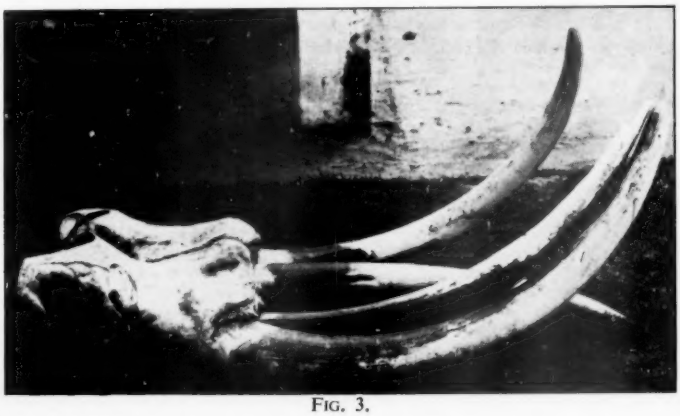

FIG. 3.

FIG. 4.

jaws show evidence of more than two dentitions, viz. vestiges of a pre-milk and a post-permanent dentition (Kükenthal, Röse, Leche, Woodward, &c.). It is also a point of interest that one tooth in each row of unerupted teeth has 'permanent' characters and the rest 'milk', and this supports the view of those who hold that the 'permanent' molars really belong to the milk dentition".

Marett Tims refers to the case in the eighth edition of Tomes's Dental Anatomy (1923), p. 314, as "an interesting example of polyphyodontism". By polyphyodontism is generally understood, to quote Marett Tims, "The perpetual replacement of teeth lost or shed in regular course which characterizes the dentition of fish and reptiles".

In the discussion which followed the paper J. G. Turner thought that the case should be placed in the class known as "polygnathism", in which one or both jaws were more or less doubled, probably a teratomatous tumour.

In 1938 the Kilmarnock District Dental Society presented to the Museum a mandible of a sheep with an accessory mandible attached (Fig. 2). The deciduous teeth are in place in the functional jaw. The accessory jaw is much distorted, the left and right halves being practically parallel with one another, the lowest row of teeth belonging morphologically to the right side. In this jaw there is a replica of the condition which was present in the mandible of the child and which would seem more correct to regard as being of the nature of a teratoma than as an example of polyphyodontism.

Herbst and Apffelstaedt (1930) describe this condition as "augnathus". They also illustrate a model of the lower milk dentition of a child with a rudimentary jaw on the right side, the rudimentary jaw carrying a single row of teeth. Adami (1909) refers to the condition as "*Dignathia*" or reduplication of the lower jaw.

During the past year the Museum has received a photograph of a rare variation of the tusks of elephants. The photograph (Fig. 3), for which we are indebted to Captain C. R. S. Pitman, shows part of the cranium of an African elephant shot at Lukaka in the territory of Kasongo, Province of Kivu, Belgian Congo. There are two tusks in each premaxilla; on the right side they run almost side by side and appear to be similar in shape; on the left side the tusk near the middle line is deflected downwards but appears to be almost similar in shape to its fellow. The animal was one of a troop of twenty and was shot by a native hunter. In the Uele elephants with four tusks are called "Siyambi" and are considered to be the leaders of the troop.

There are three specimens in the Museum which shed light upon the origin of duplicate tusks. In one, the two portions are of unequal size and where the surfaces are in contact each portion is somewhat S-shaped (Colyer, 1936*a*). The second (Fig. 4) shows a stage in the production of twin tusks. It is about two feet in length and is grooved on both sides. The third specimen was contained in the Hunterian Collection but was lost from enemy action, only a drawing now remaining (Colyer, 1936*b*). The left incisor was just protruding from the socket and was indented longitudinally. Had it continued to grow it would have resembled the specimen shown in Fig. 4. The right incisor which had been lost from the skull presented a similar condition.

Double tusks may be regarded as variations, that is they are of developmental origin. In some cases they are probably the result of dichotomy of the tooth germ. They are in a different category to the bundles of tusks consisting of several small tusks of varying sizes which are the result of injury during the formative stage of the tusk, there being four examples[1] in the Odontological Museum.

The third specimen consists of a selection of teeth (Fig. 5) which are exostosed and have been boiled in a solution of caustic potash. The teeth were placed in the solution with the object of ridding them of blood and other material. Unfortunately, they were boiled too long and when examined a few days subsequently the exostosed part could be easily separated from the surface of the root; the line of separation is clearly shown in the illustration. I had always visualized the exostosed part as being an outgrowth of the cement covering of the root but from the condition of these teeth it would seem that there is a layer of tissue of a non-calcified nature between the root and the new tissue.

These "mutilated" teeth open a field for speculative thought about the functions of the tooth sac. To quote from Tomes (1923): " It is said that the inner layer of the tooth sac is concerned in the formation of cement; that the outer layer, conjointly with the surrounding connective tissue, is converted into the alveolar-dental periosteum." But in addition there is some evidence that the lamina dura (the layer of bone bordering the tooth socket) is also formed from the tooth sac. In the skull

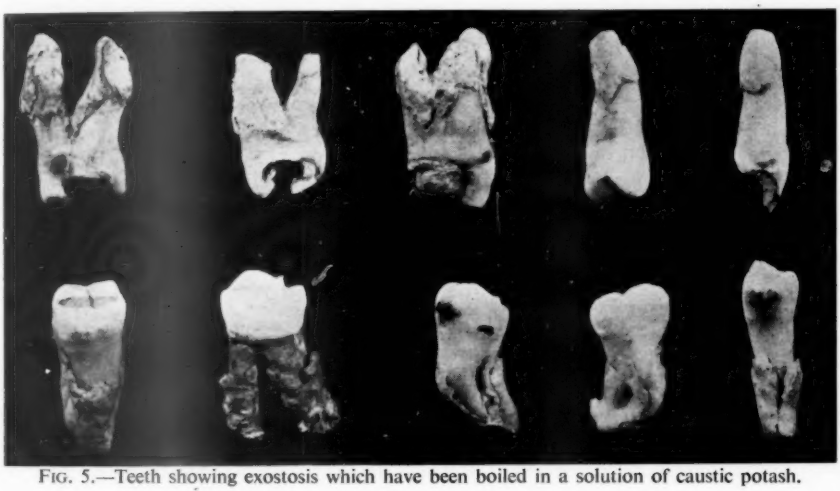

FIG. 5.—Teeth showing exostosis which have been boiled in a solution of caustic potash.

of a cyclops sheep in the Odontological Museum (Fig. 6) the developing molar is seen projecting into the zygomatic fossa surrounded by a layer of bone which is quite independent of the bone of the maxilla. It seems to me that this bone can only have been formed from the tooth sac. The formation of a layer of bone around developing teeth, which is independent of the jaw, is well illustrated in the mandible of the young manatee and a similar condition can be observed in the young pig, walrus and other animals.

The cells of the tooth sac may be regarded as arranged in three layers: one, the innermost, which in time undergoes calcification and forms cement, a middle layer which does not undergo calcification and forms the periodontal membrane, and an outer layer which, in time, does undergo calcification and forms the lamina dura. In inflammatory conditions of the periodontal membrane the cells undergo proliferation, and the fact that in these exostosed teeth the new tissue can be separated from the cement of the roots suggests that those cells immediately adjacent to the cement correspond to the middle layer of the tooth sac, the new tissue being formed from the outer layer of cells which does undergo calcification.

It is only on such lines that a satisfactory explanation can be provided of the condition seen in the specimen shown in Fig. 7 which was described by Bland-Sutton (1888) as a radicular odontome in a horse. An examination of the specimen brings out clearly that it is the result of an extensive inflammatory reaction following a severe injury to a developing tooth. The positions of the third and fourth premolars are occupied by a large mass of dental tissues. The tumour has expanded the bone which also shows signs of inflammatory reaction and is pierced in places by sinuses. The second premolar has not erupted; it is stunted in its growth and is covered with a thick layer of cement. The molars are missing from the specimen but their positions are indicated in the illustration. The greater

[1] G.136.2, G.132.21, G.132.22, G.132.23.

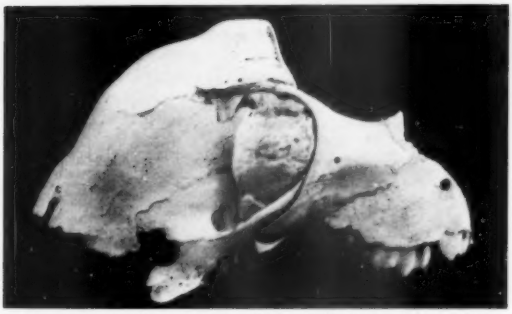

FIG. 6.—The cranium of a cyclops sheep. Roy. Coll. Surg. Mus. Odonto. Sect. G.5.1.

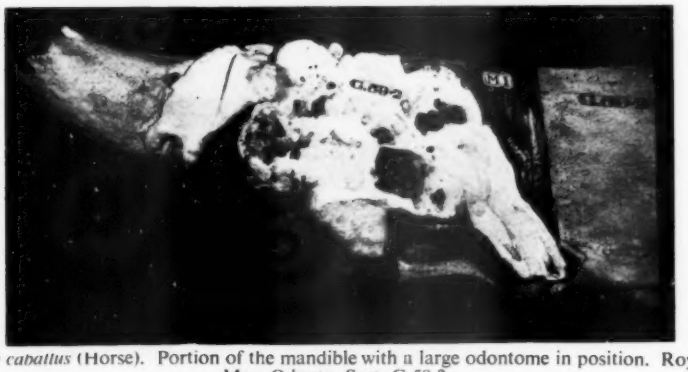

FIG. 7.—*Equus caballus* (Horse). Portion of the mandible with a large odontome in position. Roy. Coll. Surg. Mus. Odonto. Sect. G.59.2.

part of the mass is composed of a cement-like substance in which there are numerous irregularly shaped cavities. At the antero-inferior part the third premolar has been cut in an oblique direction and the postero-inferior part of the fourth premolar has been divided in a longitudinal direction; both these teeth have been displaced downwards so that their lower borders are covered only by the bone of the jaw. The third premolar appears to be normal in type but the fourth premolar is distorted, the upper part being bent back on the lower portion which shows signs of having been split in a longitudinal direction. The bony wall surrounding the odontome is very irregular and when first examined by Bland-Sutton there were several small masses of calcified tissue embedded in the bone.

In this specimen, although there is evidence of inflammatory reaction in the soft tissues of the tooth and surrounding bone of the jaw, there are no signs of ankylosis of the mass to the jaw. This separation can only be explained on the basis that the tooth sac has the three functions as outlined above. The tissue embracing the misplaced teeth would be derived from the inner cells of the tooth sac and the small masses of calcified tissue embedded in the bone from the outer cells, that is from cells which may undergo calcification; intervening between these would be cells which do not undergo calcification, the function of which is to form periodontal membrane.

But, even if, as seems probable, these small masses and the new tissue on exostosed teeth are the product of the outer cells of the tooth sac, an explanation is still needed to account for the fact that these tissues are not ankylosed to the surrounding bone. We need more knowledge of the structure of the lamina dura and its connexion with the body of the bone before a complete explanation can be given of the conditions seen in these specimens.

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Section of Surgery

President—DAVID H. PATEY, M.S., F.R.C.S.

[*April* 2, 1952]

DISCUSSION ON THE TREATMENT OF CERVICAL METASTATIC CANCER

Dr. Hayes Martin[1]: In each of the separate anatomical varieties of carcinoma of the mouth and pharynx the treatment techniques (surgical or radiological) differ or vary greatly. Most published reports are largely limited to discussion of the primary lesions and little consideration is given to what is actually the major problem and one common to all forms of head and neck cancer, namely the management of cervical metastases. Neck dissection has now become a standardized operation. Although there are many recorded cures of histologically proved cervical metastases by radiation therapy, nevertheless, in actual practice, neck dissection is generally accepted as the most effective method of treatment.

The indications for neck dissection are:

(1) There should be definite clinical evidence that cancer is present in the cervical lymphatics. (Acceptance of this belief will immediately rule out so-called "prophylactic neck dissection".)

(2) The primary lesion giving rise to the metastases should have been controlled clinically or, if not controlled, there should be a plan for removal of the primary at the same time that neck dissection is performed.

(3) There should be a reasonable chance of complete removal of the cervical metastatic cancer.

(4) There should be no clinical or X-ray evidence of distant metastases.

(5) Neck dissection should offer a more certain chance of cure than radiation therapy. (It generally does, but under certain circumstances—as where a primary lesion is anatomically inoperable—irradiation of the neck is the method of choice.)

Certain supposed contra-indications are often mentioned in reports on neck dissection. For example it has been said that bilateral cervical metastases constitute a contra-indication to neck dissection. This idea has been based upon erroneous belief that bilateral complete neck dissection is not a safe procedure. This has been disproved.

A rational plan for the operation must be based upon a correct and reasonably thorough understanding of the cervical lymphatics. (The various superficial and deep lymphatics and groups of nodes were described. Detailed slides of the technique of the operation were shown.)

The following table of results was given:

FIVE-YEAR END-RESULTS IN NECK DISSECTION

(Neck dissection alone, combined procedures not included)
Head and Neck Service, Memorial Hospital. 1928 to 1945, inclusive

Total patients		334
Indeterminate results		
Dead from other causes without recurrence	28	
Lost track of without disease	3	
Total indeterminate results		31
Determinate results		
Total number minus indeterminate results		303
Failures		
Post-operative death	10	
Lost track of with disease	2	
Dead as a result of cancer	177	
Dead of other causes, cancer present	3	
Living with cancer	4	
Dead—presence of cancer unknown	3	
Total number of failures		199
Successful results		
Free of disease at five years from neck dissection		104
Net Five-year end-results		
Successful results divided by total determinate results (104/303)		34·3%

[1] Abstract. Published by permission of the Editor of *Cancer*. For detailed elaboration of this paper *see* Martin, H., Del Valle, B., Ehrlich, H., and Cahan, W. G. (1951) *Cancer*, **4**, 441.

Dr. A. Tailhefer (Chirurgien de la Fondation Curie, Paris; Membre de l'Académie de Chirurgie): The statements I shall make on this subject represent the opinions of the workers at the Fondation Curie—opinions based on a large number of cases, which have been treated since 1919 by Mr. Roux-Berger and myself. Mr. G. Gricouroff has been largely responsible for the histology and Mlle J. Baud has treated most of the primary tumours by radium needles. My thanks are also due to Mlle Baud for the statistics involved in the work.

Cancer of the tongue.—Our technique of neck dissection was inspired by Maitland and Crile: and Figs. 1–4 give a clear idea of the method.

This neck dissection is usually practised under local and regional anæsthesia, a fact which enabled us to reduce the operative mortality rate to 1%. This is of primary importance in justifying our operative indications.

The operation is a block dissection of the area concerned, clearing first the submental and submaxillary areas in a backward direction, then the supraclavicular and carotid areas upwards from the clavicle to the vicinity of the base of the skull.

Practised in such a way, this wide ablation of the lymph nodes involves the sacrifice of the sterno-cleido-mastoid muscle and the internal jugular vein. It is possible to insulate and preserve the ramus cervico-facialis in order to avoid facial paralysis. It is even possible (Dargent and Redon) to keep the spinal accessory nerve, the section of which causes a disastrous atrophy of the trapezius, especially in the case of a so-called prophylactic operation.

When both sides of the neck must be operated on, we practise two successive operations with an interval of one or two weeks and we preserve the internal jugular vein on the less injured side: the dissection of the lymphatic plane is easy enough, provided we keep in close contact with the wall of the vein. Both of the internal jugular veins can be removed without causing serious disorder only if the two operations are carried out at an interval of several months, and even then it usually causes for a while an œdema of the face on the side last operated on.

For cancer of the lips we reduce this operation to the dissection of the submental and submaxillary areas, generally on both sides.

The Importance of Neck Dissections

Treatment of cancer of the anterior part of the tongue.—Each cancer has its individual characters, its particular mode of local evolution and lymphatic extension. Some adenopathies are radio-sensitive, others much less so, as in the case of cancer of the anterior part of the tongue. *They remain primarily within the range of surgical therapy*, and the same may be said of adenopathies following cancer of the lips.

The first French authors to write on the subject, Poirier, Morestin, then Sebileau, Cuneo, were in favour of neck dissections in all cases, whether there were palpable cervical metastases or not. In this they enunciated one of the fundamental rules of cancerology: namely that in any cancer susceptible of lymphatic metastasis, therapy must be directed, not only to the primary tumour, but also to the corresponding lymphatic area. Should this idea be revised in the case of cancer of the tongue in particular? We do not think so.

It is true that, in some fortunate cases, a cancer which is still well localized can be cured by a conservative treatment or operation, and, faced with such a result, it seems but natural to regret, in apparently similar cases, one's recourse to more drastic measures. When the post-operative pathological report does not show the presence of any metastatic cell in the lymph nodes, one may be inclined to criticize neck dissection.

Yet, before the dissection, we cannot tell the actual extent of a malignant tumour, nor judge its histological spread. Even with a negative report, it is impossible to be certain that one of the sections not examined may not contain evidence of malignancy. Therefore the rate given of metastasis in the lymph nodes is probably very much below the actual rate.

On the question of cervical metastasis in the case of cancer of the tongue are the clinical reports sufficiently ample to permit of our arriving at definite conclusions?

The facts observed at the Fondation Curie are as follows:

(1) Out of 182 cases (Table I), in which the lymph nodes felt in the neck seemed to be clinically cancerous, 61 (or 34%) proved to have histologically negative lymph nodes, namely one-third of the cases.

(2) Out of 244 cases (Table II), in which, on the contrary, there were no clinically suspicious nodes, the latter were histologically positive in 106 cases (or 43%), namely in nearly half the cases.

At this stage, the involvement is usually only partial.

The clinical report of the lymphatic areas, except in cases of far-advanced adenopathies, does not then convey any precise information. It does not therefore seem acceptable to stake the future of the patient on such uncertain findings.

It might yet be thought that a systematic careful observation of the patients could give valid and useful information, that a growth, still small at the time of a first examination, will reveal its malignancy somewhat later through a progressive increase. But this is often illusive: for a long time no

FIG. 1.—Incision.

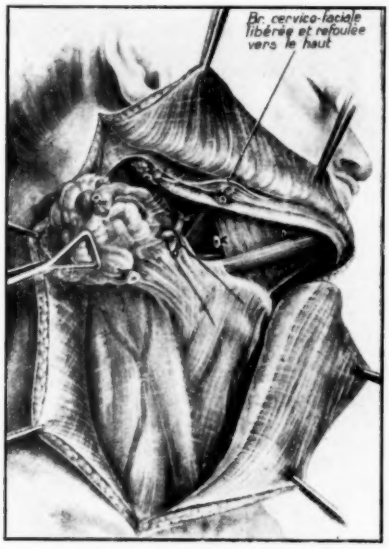

FIG. 2.—Submaxillary dissection.

FIG. 3.—Carotidian dissection.

FIG. 4.—Upper ligature and section of the internal jugular vein. The posterior belly of the digastric muscle has been excised in order to extend the operative area upwards.

adenopathy can be felt and then the latter will often develop very rapidly. In the space of a few weeks, if not of a few days, the adenopathy will no longer be operable, or, if so, only under bad conditions, and the operation, as I am going to show, will then have nothing but evil results.

To wind up, I shall now discuss the only elements susceptible of giving any valid conclusions, that is, to examine the five years' results in a total of 426 cases, a number large enough to allow of the establishment of significant percentages.

In all those cases, neck dissections were systematically performed, whether or not there were lymph nodes palpable at the beginning of the treatment. The nodes have always been examined histologically. Tables I and II give our results.

TABLE I.—NECK DISSECTIONS WITH NODES FELT AT FIRST EXAMINATION

Hist. negative nodes	Hist. positive nodes	Total of cases
61 (34%)	121 (66%)	182
Cured	Cured	Total of cured
22 (36%)	14 (11·6%)	36 (20%)

TABLE II.—NECK DISSECTIONS, NO NODES FELT AT FIRST EXAMINATION

Hist. negative nodes	Hist. positive nodes	Total of cases
138 (57%)	106 (43%)	244
Cured	Cured	Total of cured
65 (47%)	28 (26%)	93 (38%)

I.—CURATIVE VALUE OF NECK DISSECTIONS

Tables I and II, 2nd column, permit a very clear conclusion. With prophylactic neck dissections, one-fourth of the cases (26%), have been cured, cases in which lymphatic metastasis was still only in the microscopical stage and without any clinically perceptible adenopathies. On the other hand, when the neck dissection was applied to really malignant and palpable adenopathies, only one-ninth of the cases were cured (precisely 14 out of 121, that is 11·6%).

These differences are material enough for us to conclude that neck dissection is a useful operation for very small lymphatic metastases still in their microscopic stage, whereas its results are poor for more evolved tumours that have become palpable.

II.—IMPROVEMENT OF THE RESULTS DUE TO PROPHYLACTIC NECK DISSECTION

If we had allowed the lymphatic metastases to develop, those 106 cases (Table II) would have been operated upon later, only after the clinical appearance of the adenopathies.

At that time, we could have hoped to cure only 11·6% of the patients (Table I), 12 cures instead of 28. Prophylactic neck dissection registers 93 cures out of a total of 244 patients, without palpable adenopathies, namely 38%. A delayed operation, after the appearance of the adenopathy, would theoretically have made us lose 16 patients (28 minus 12), and we should then have registered only 77 cures (93 minus 16) out of 244 patients.

Prophylactic neck dissection would appear to allow a gain of 6%, an important point, since the most favourable percentages of five years' cures do not reach 50%.

III.—OTHER POSSIBLE AMELIORATIONS—PRESENT METHOD OF TREATMENT

It is difficult, from a close study of the observations made, to allow exactly for the different causes of failures in the treatment of cancer of the tongue.

We had long thought that such failure was mostly due to the treatment of the lymph nodes. To-day we think that bad results are very often the consequence of the lingual recurrence itself. Tables I and II (column 1) show that in cases of negative lymph nodes, the cures amount only to 36% (in cases with palpable adenopathies, theoretically less favourable) and to 47% (without palpable adenopathies, theoretically more favourable). Both these series with negative lymph nodes come to a total of 199 cases with only 87 cures and thus, lingual tumours without lymphatic metastasis have been cured in only 44%.

The improvement of lingual cures is therefore our first objective, so I am going to try and complete the action of the usual radium needling by an excision of variable width (but not too mutilating) of the initial area of the cancer by means of cutting electro-coagulation: this excision will be performed six or eight weeks after the radium needling, at the same time as the neck dissection which may, without inconvenience, be postponed, unless the adenopathies are too serious. With such excisions, ligature of the external carotid artery is indispensable and usually on both sides. This insured against serious post-operative hæmorrhages chiefly from the tenth to the fifteenth day. I may thus be able to perform neck dissection with greater assurance as regards the cure of the primary tumour, whose original nucleus is very likely more radio-resistant than the peripheral extension. It is obviously desirable that the tumour of the tongue should be ablated at the time of the neck dissection.

IV.—Indications for Bilateral Neck Dissection

In an earlier publication with Roux-Berger, we showed that a metastasis in the lymph nodes on the opposite side to the lingual tumour was to be noted only in 6% of the cases as long as the tumour was well lateralized, but that it was found in 32% of the cases when it bordered upon, reached or passed the medial line. A bilateral neck dissection is indicated in such cases, which include cancer of the tip of the tongue. We then have two consecutive operations at an interval of one or two weeks.

Treatment of cervical metastasis in cancer of the lips.—As I have already observed, the treatment of these adenopathies can be studied only with reference to the cancer whose metastases they are.

Cancer of the upper lip is rare. It is most often a basal-cell carcinoma, which occurs on the skin of the lip and never spreads through the lymph nodes. Should the cancer be on the mucosa of the lip, it is then a squamous-cell epithelioma, like cancer of the lower lip, and consequently may spread through the lymphatic area.

Metastases in the lymph nodes are less frequent than with cancer of the tongue. When the tumour is superficial and scabby, it is useless to have recourse to a neck dissection, unless an adenopathy is obviously existing. When the tumour is ulcerous and infiltrating and especially if it involves the mucous part of the lip, then we should recommend a neck dissection, even without palpable adenopathy.

The operation will then be restricted to the submental and submaxillary areas on both sides of the neck, except if the tumour is well lateralized and well away from the medial line. When the tumour reaches the commissure and spreads along the internal surface of the cheek, it will then be preferable to have a submental, submaxillary and carotidian dissection. The adhesions in submaxillary metastases are no contra-indication; it is generally possible to detach the glands from the bone by using the subperiosteal plane of cleavage with the help of a raspatory.

Out of a total of 287 cases of squamous-cell epithelioma of the lower lip treated by radium or X-rays:

154 have not undergone any treatment of the lymphatic areas, giving 94 cured (61%);

55 have undergone irradiation of the lymphatic areas, giving 17 cured (31%);

78 have undergone neck dissection: in 35 the nodes were negative, giving 22 cured (63%); in 43 they were positive, giving 14 cured (33%).

Among the patients that have not been cured, 28 (10%) died of the cervical metastasis, the lip having healed from five months to three years earlier.

15 among these 28 had undergone a neck dissection, 14 with positive lymph nodes, 1 with negative.

11 had been treated with radium for adenopathies which in 9 cases had been judged as beyond an operation.

1 had undergone no treatment of the lymphatic areas.

1 had refused treatment.

Sir Stanford Cade: The material on which I base my opinion as regards treatment of cervical metastatic cancer consists of a total of 1,428 patients with primary cancer in the mouth or neck.

Table I shows the anatomical site of the primary growth.

Table I.—Site of Primary Growth. 1,428 Patients (1925–1951)

Lip	126	Nose	18
Tongue	465	Nasopharynx	36
Mouth floor	118	Tonsil	85
Gum	35	Pharynx	209
Cheek	55	Larynx	158
Palate	97	Thyroid	26
Total	896	Total	532

The study of these patients showed clearly the difference in the liability to metastatic lymph spread from various primary sites.

Table II shows the incidence in cancer of the various sites in the mouth.

Table II.—Incidence of Lymph-node Metastasis

Primary site	Percentage incidence
Lip	27
Tongue	65
Mouth floor	50
Buccal mucosa	40
Palate—hard	30
Palate—soft	60

The figures indicate the state of the neck lymph nodes at the time of the first attendance of the patient. The subsequent history of the patients shows delayed involvement of the cervical lymphatics in many patients, even when the primary growth had been adequately dealt with. Periods of delay in the appearance of lymph nodes varied from a few months to many years. In the majority of patients

lymph nodes became palpable within eight to fourteen months. There are, however, quite a number of patients in whom nothing abnormal was felt in the neck for periods up to six and nine years and who then developed cervical lymph node metastasis, although the site of the original primary growth remained healed. It is important to realize that this clinically silent period of latent disease in the lymph nodes is not entirely a mysterious haphazard and unpredictable phenomenon. It depends in some measure on known factors such as the site of the primary lesion and the histological type of the tumour. It is well known that intrinsic lesions of the larynx are the least prone to metastasize, that lip cancer is as a rule less likely to spread than tongue cancer, that the hard palate and the soft palate show a marked difference, the latter metastasizing twice as frequently as the former. It is also generally accepted that histological grading according to the degree of anaplasia or keratinization is of some importance. Yet the problem of the choice of treatment to the neck still presents considerable difficulty.

Choice of Treatment

To simplify this problem certain points should be kept in mind. In their relative importance they are as follows:

(1) Site of primary lesion.
(2) Response of the primary lesion to treatment.
(3) Clinical state of lymph nodes.

The site of the lesion is the best-known factor and most experienced clinicians assess this accurately. To take extreme examples: the lip affords a considerable margin of safety in contrast to the sinus pyriformis where the lymph node spread is early and rapid.

The response of the primary lesion to treatment is of importance. Little if anything is gained by treatment directed to the lymph nodes if the primary growth is not controlled. The propriety of inflicting anything but palliative treatment to the neck in the presence of an uncontrolled lesion in the mouth is very doubtful.

The clinical state of the lymph nodes is the key to the choice of treatment. Before analysing in more detail how the state of the lymph nodes affects the decision, it is necessary to consider what treatment is available.

Type of Treatment Available

Metastatic cancer in the neck can be controlled and has, in fact, been controlled by radiotherapy. Without entering into the technical details as to the various methods of irradiation applicable to the neck, it is admitted that complete disappearance of lymph-node metastasis has been achieved by radiation. Yet the effect of radiotherapy on any tumour, except the most radiosensitive anaplastic type, is unpredictable and I share Hayes Martin's view that "that procedure should be used *initially* which yields the highest percentage of cures in the greatest number of patients." Such a procedure will depend upon the state of the lymph nodes; if these are fixed to the vascular sheath and considered inoperable, although the nodes may in fact be removable, surgery has not proved of value and local recurrence is the rule. If the lymph nodes are free and mobile a radical neck dissection—the so-called block dissection—is the method of choice. This, however, should only be undertaken if the primary lesion is healed. If no lymph nodes are palpable in the neck there is the choice between the so-called "prophylactic" neck dissection and no treatment, providing the patient can be kept under observation and examined at regular intervals. The case for observation seems to me to be stronger than the case for prophylactic block dissection. The latter practice would inflict a number of unnecessary or avoidable operations; unnecessary in the absence of metastasis, avoidable in the presence of local disease.

In the treatment of lymph-node metastasis by surgery nothing but a radical dissection or "block" should be done. There is really no indication for partial removal of lymph nodes, the upper or supra-hyoid dissection or any other limited operation. Very little is gained by such conservatism and often by limited operations the chance to eradicate the disease is missed. It is necessary in my opinion to have definite criteria when a radical "block" dissection is to be done. These criteria are as follows:

(1) The primary lesion should be healed.
(2) The lymph nodes should be palpable but strictly operable.
(3) The general condition of the patient must permit of a major operation. Age by itself is not a contra-indication.

Bilateral block dissection is indicated when bilateral lymph nodes are present. The removal of both internal jugular veins seems to be safe; the operation is preferably done in two stages at an interval of two weeks, but both sides have been operated upon at one sitting without any intracranial complications. There are a few points in the technique of the radical dissection which justify emphasis: it is, of course, essential to remove the internal jugular vein and sternomastoid muscle and no attempt at their preservation is permissible—this, of course, is, or should be, well known. The preservation of the spinal accessory nerve is not justifiable as no adequate clearance of the posterior triangle of the neck can be done if the nerve is preserved.

The mortality of the operation varies from 1 to 3% in various clinics. In the past six years in my own personal series of 48 radical neck dissections there has been one operative death. The morbidity following the operation is chiefly due to the spinal accessory paralysis—it is as a rule limited. Œdema

of the face and slight palsy of the lower facial branch are transient phenomena. Women stand the operation just as well as men.

Prophylactic radiotherapy to the neck in the absence of palpable lymph nodes is not practised. Post-operative radiation is of benefit when many lymph nodes are involved.

The indications for radiotherapy in preference to surgery are as follows:

(1) When the primary lesion has not entirely regressed.

(2) When the lymph nodes are fixed to the main vascular sheath or adherent to the deep cervical fascia.

(3) When the general state of the patient does not permit a major procedure.

Professor B. W. Windeyer agreed that surgery was the best treatment for metastatic glands in the neck, with certain exceptions—notably when the site of the primary lesion was in the nasopharynx or maxillary antrum. These cases, even when operable, were better treated with radiotherapy. He believed in a "wait and see" policy if the patient could be kept under observation.

Sir Gordon Gordon-Taylor was impressed by the vast number of cases operated on in U.S.A. and France. He noticed the discrepancy between the two first speakers, Dr. Hayes Martin having a five-years survival rate of 34% of cases operated on when the glands were involved, and the survival rate of Dr. Tailhefer which was not quite as good, even though many prophylactic blocks had been done which would obviously improve his figures. Sir Gordon stated that he was in the habit of removing the posterior belly of the digastric, so that all glands could be cleared up to the base of the skull, and of removing the lower part of the parotid gland. He had a preference for chloroform as an anæsthetic and felt that blood transfusion was rarely necessary after this operation. He was glad to see cases operated on where the primary growth in the jaw was excised in one piece with a block dissection of the neck. These were very grave cases, but the outlook had been better since the use of penicillin. He was pleased to hear the operation associated with the name of Maitland of Sydney.

Dr. Hayes Martin, in reply to the discussion, stated that the logical conclusion concerning prophylactic block dissection is that it should be done on both sides of the neck.

He stressed that adhesions to local structures such as mandible, internal jugular vein and external carotid artery, do not necessarily exclude block dissection.

He considered that hypotensive anæsthesia entails dangers; that it was unnecessary to remove the posterior belly of the digastric muscle.

He considered that block dissection of the neck should be done for secondary deposits appearing after unsuccessful radiotherapy of nasopharyngeal nodes.

He said that the lower pole of the parotid was removed and thought that blood transfusions were of additional value in making recovery more speedy.

Dr. Tailhefer said (in answer to Dr. Hayes Martin) that the treatment of cervical metastatic cancer must be discussed with regard to one type of cancer exclusively. Each type presents its own features, its own local and lymphatic extension. This was the reason why he centred his present lecture on the cervical adenopathies of cancer of the anterior part of the tongue. Prophylactic block dissection should not necessarily be undertaken on both sides of the neck in all cases: well-lateralized tumours metastasize to the opposite side in 6% of the cases only, whereas tumours reaching or passing the medial line of the tongue metastasize to the opposite side in 32% of the cases; therefore, bilateral prophylactic block dissection should be done only in the latter type of tumour which includes cancer of the tip of the tongue. He stated that removal of the digastric muscle made the operation easier and more complete.

Sir Stanford Cade stated that hypotensive anæsthesia with C5 does not produce anoxia and that the patient's head can be raised when using it. He considered it a technical advance of very great value, and proof that it could be used in head and neck surgery was provided by the plastic surgeons.

[*May* 7, 1952

Meeting at the Middlesex Hospital, W.1

Operations were performed by Mr. R. S. Handley, Mr. Holmes Sellors, Mr. O. V. Lloyd-Davies, Mr. E. W. Riches, and Mr. W. R. Winterton.

The following short papers were read:

The Prevention of Post-operative Pulmonary Collapse.—Dr. B. A. Sellick and Dr. K. N. V. Palmer.

Peroperative Cholangiography.—Mr. A. W. Nurick.

A Follow-up of Cases of Vagotomy for Peptic Ulcer.—Mr. B. H. Hand.

Hæmorrhage from Peptic Ulceration as a Complication of Intestinal Intubation.—Mr. L. P. Le Quesne.

Hiatus Hernia Associated with Carcinoma of the Œsophagus.—Mr. J. R. Belcher.

X-ray Investigation of Retroperitoneal Swellings.—Mr. I. H. Griffiths.

The Early Diagnosis of Carcinoma of the Pelvic Colon.—Mr. J. H. L. Ferguson.

Dupuytren's Contracture.—Mr. J. S. Golding.

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Section of the History of Medicine

President—LILIAN LINDSAY, C.B.E., LL.D.Ed., L.D.S.Ed., M.D.S.U.Durh., F.D.S., H.D.D., R.C.S.Ed.

[*June* 4, 1952]

Homer as a Surgical Anatomist [*Abstract*]

By A. RALPH THOMPSON, Ch.M., F.R.C.S.

THOUGH Homer composed his poems nearly 3,000 years before the present day, yet he shows a wonderful knowledge of anatomy and is not only exact, but—as might be expected—very felicitous in the descriptions of the wounds which he supplies.

Homer describes enough wounds for statistics to be made from them, but it is sufficient to say here that of the various wounds, about 150 in number, the perforating wounds are five times as common as the incised which, in turn, are twice as common as the contused. There is only one wound noted as having been made by an axe.

In only one case, noted by Homer in the *Iliad*, is blindness recorded, and I cannot find a single case mentioned in the *Odyssey*—very few indeed compared with what is found in Milton's poems.

It is curious that although Homer knows about the manufacture and use of steel, he does not mention it in connexion with war-weapons. He does not mention a single case of left-handedness. Mutilation of people is noted as being done after death. Poisoning either of weapons or of food was known to Homer. He dislikes a bent weapon and will not describe any wound made by such: in fact, Homer likes levels and describes them very accurately. But before these levels are briefly dealt with, two excellent pieces of anatomy may be mentioned. The first case is that of the fatal wound which was inflicted upon Hector by Achilles: "There was an opening where the collar bones coming from the shoulders clasp the neck even at the gullet, and there Achilles drave at Hector with his spear, and right through the tender neck went the point, yet the bronze-weighted ashen spear clave not the wind pipe so that he could still speak, and fell in the dust." We may note that the indefinite word "throat" is not mentioned. The description of the clavicle is very good and the accuracy with which Homer notes that the larynx escaped being wounded is admirable. The next case is even better in its anatomy and whilst it is absolutely correct it is entirely unexpected. I am not sure that a candidate at one of the higher examinations would like a man to be set before him with his back turned to him and be asked to mark out the urinary bladder in relation to the buttock, but Homer certainly knew of the relationship of the two structures. Meriones shoots an arrow through Harpalion's right buttock, and the arrow is said to have gone right through the bladder and to have emerged under the bone, i.e. the pubic bone. The weapon would enter about the middle of the right buttock and pass through the great sacro-sciatic notch, enter the pelvis, pass through the base of the bladder and come out under the pubic arch. It may be wondered if Homer knew that an arrow entering the right buttock would not wound the lower end of the colon and the sigmoid.

Another of his descriptions shows that Homer knew that it would be necessary to divide the clavicle before a forequarter amputation: Diomed slays Hyperion "by smiting with his great sword upon the collar bone. Beside the shoulder he smote, and severed the shoulder from neck and back". In other words, Diomed performed a clean forequarter amputation. He must have gone internal to the shoulder or deltoid region "beside the shoulder", for to have gone external to the shoulder would have been simply to have cleft the air.

Very different from this account is one where we are told that the point of the spear rent the root of the arm from the muscles and tore it to the bone; here Homer's account is not so anatomically exact as is usual with him.

That Homer recognized the various parts, central and peripheral, of the nervous system is indicated by his mention of the brain on frequent occasions, sometimes as not being damaged though the wound might be immediately adjacent to the brain. He also mentions the spinal cord and when Achilles decapitates an opponent it is said that the marrow rose out of the back bone. The peripheral nervous system is implied in the following passage: "Teucer drew back his bow to shoot at Hector, who picked up a jagged stone, and hurled it at Teucer, and hit him beside his shoulder, where the collar bone fenceth off neck and breast, and where is the most deadly spot. The bow-string was broken and his hand from the wrist grew numb." Clearly the brachial plexus or part of it was damaged.

Two cases of good anatomical description have now been considered, and also one case where the anatomy was suggested. We now come to consider two cases of what I may call speculative anatomy—not that Homer does not describe the topography of the wound, but he does not give names to all the structures which were damaged. Diomedes cast a stone at Aineias. The stone was a heavy one and struck Aineias on the hip "where the thigh turneth in the hip-joint, and this men call the cupbone, so he crushed the cupbone, and brake both sinews withal, and the jagged stone tore apart the skin. The hero stayed fallen upon his knees, and with stout hand leant upon the earth, and the darkness of night veiled his eyes". Here, the kneeling position implies that the hip-joint was not dislocated although the acetabulum was broken. We are left to speculate as to the actual damage done, especially to the "two sinews" and what these were. Suspicion may be directed to the ligamentum teres, but if the joint were not dislocated this ligament was probably not ruptured. Let us therefore invoke the iliofemoral ligament which, in its lower three-fifths, is distinctly double, and both parts would be damaged by such a blow as Homer here describes.

The second instance of speculative anatomy is as follows: A jagged stone was hurled at a warrior and is said to have hit him on the right leg "hard by the ankle, and it crushed utterly the two sinews and the bones". The identity of the bones is obvious, but which are the "two sinews"? Not, probably, interosseous ligaments, for these could hardly be described as sinews, and one may suspect that the two sinews in question were the tendo Achillis and the thick tendon of the tibialis anticus which forms almost as distinct a prominence as the tendo Achillis itself. Whilst in the ankle region, we may refer to the post-mortem wound inflicted by Achilles on Hector, whose tendo Achillis on each side was pierced or slit "from heel to ankle joint"; here Homer has not indicated that the ankle-joint is a mortice, and therefore cannot have only a single level in its upper part. "The tendons of both feet behind he slit from heel to ankle joint, and thrust therethrough thongs."

Homer takes the trouble to mention, in his descriptions of wounds, whether the bone was broken or whether the injury was adjacent to bone; we have already considered examples of compound fracture or dislocation. But Homer also pays some attention to wounds that merely grazed or scratched the bone. Some examples of all three types are as follows: One warrior "drave the bronze clean through the thigh, and the spear brake the bone". A Grecian "smote Sarpedon with his long spear, and the point sped through furiously, grazing the bone". Another warrior's shoulder was hit "and the spear point scratched the bone". Finally there is the case of Odysseus, who, as a boy, was wounded by a boar, but according to Homer the boar's tusk did not reach the bone. Thus a classification might be made of wounds which broke, grazed, or missed the bone completely.

As far as wounds of the abdomen go, Homer has upper, middle, and lower levels exactly comparable to those of Cunningham. He draws attention to the special danger of wounds inflicted below the navel. Homer shows that he knew that the liver lies below the diaphragm and that the lungs and heart lie above it. There are four cases of wounding of the liver through the abdominal wall, and in one of these cases it is stated that the liver dropped out of the body on to the ground. The liver must have rolled right out of its usual position, it was not merely the apparent moving downwards of the liver which is really its rotation on a transverse axis. The description of this wound shows that Homer knew of the possibility of hæmatoma of the chest following an abdominal wound, for when the liver dropped to the ground "black blood filled the bosom". Only one wound of the liver is mentioned in the *Odyssey*, where the weapon, an arrow, pierced the chest above the diaphragm. In two cases Homer states that the lungs were wounded, and in one of these the point of entry of the weapon is said to lie above the pap. Two wounds of the heart are described and both are interesting. One of them describes what must be the first recorded instrumental examination of the heart: "Idomeneus smote his opponent in the breast with a spear and rent the coat of arms about him, and he fell with a crash, and the lance fixed in his heart, that still beating, shook the butt end of the spear." The second wound of the heart is described when Patroclus struck Sarpedon with a sword "where the midriff clasps the beating heart . . . and Patroclus drew the sword out of Sarpedon's flesh and the midriff followed with the sword". Here the midriff includes the pericardium.

Homer's transverse levels of the abdomen—upper, middle, and lower—have been referred to, but there are also vertical levels through the navel and along the flank. Homer also realized the relationship of the back to the abdomen. He knew, too, of the importance of the peritoneum, because he notes particularly when the bowels escape from a wound. In one case, Homer tells how a wounded man ran about the battlefield, holding up his bowels; and that such a wound need not be immediately fatal is shown by the fact that the wounded man's brother, Hector, led him away. That the prognosis in such a case may be actually good is shown by Xenophon who records how a leader amongst the 10,000

came into camp, after receiving an abdominal wound, holding up his bowels. This man survived to play the traitor on the Greeks and to sail off two days after his appearance in camp. There are two wounds of the flank, in one of which the wound is said to have let out the entrails, but in the second case "the spear thrust through the corselet, and though it tore clean off the flesh of the flank, it did not mingle with the bowels of the hero".

Another wound described by Homer is well worth notice: Antilochos leaped on his opponent and wounded him "and severed all the vein that runs up the back till it reaches the neck". This is the only time that a vein is mentioned by Homer, and he could, of course, be referring to the aorta, although he has already defined the clavicle as separating the neck from the breast, and the aorta does not reach into the neck. But there is a continuous venous structure running along the back, namely the right innominate vein, the superior vena cava, the right auricle, and the inferior vena cava. These together may have been the structure referred to, the vein which was severed.

In conclusion, it may be appropriate to ask the following question: Did Homer know of the frontal sinus? To answer this question in the affirmative one case may be considered: Antilochos slew a Trojan warrior, driving a spear through the helmet ridge into the warrior's brow, "and the point of the bronze passed within the bone". Here we must note first that the force of the spear blow would have been reduced by the strongly resistant helmet ridge, and that the point of the spear passed *within* the bone, i.e. into a cavity of the bone which in this region would be the frontal sinus. Secondly, we note that the brain is not mentioned, which, judging from other exact descriptions, it certainly would have been had it been wounded. I suggest, therefore, that the spear did not pass beyond the frontal sinus and that Homer realized this.

Perhaps enough has now been said to indicate that Homer knew a great deal of anatomy; I hope the subject may receive further attention in a more extended paper.

Translations used:

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Odyssey, Butcher, J. G., and Lang, Andrew. Macmillan.

Galen's Elementary Course on Bones

By Charles Singer, M.D.

The little work by Galen (A.D.130–201), **Peri osteōn tois eisagomenois,** usually known by the Latin translation of its title, *De ossibus ad tirones* "On bones for beginners", is of some interest both for itself and for its history. It was composed about A.D. 180. It is the only anatomical work surviving from antiquity that is based primarily on human material, and is the only one meant for young students. It is of the nature of a series of introductory lectures, or rather demonstrations, and gives some idea of elementary anatomical teaching in the second century of the Christian era. It survives in a single early MS., namely that of the ninth century at the Laurentian library at Florence. This is probably the only important MS. of the text in existence. There is no doubt that the work is genuine. Galen included it in his list of his own books. This by no means excludes the possibility of later changes and the text has, in fact, been subject to considerable corruption, to some omissions and, I think, has some insertions. Nevertheless the existing state of the text gives a very fair idea of an ancient first course for beginners and is a fair example of Galen's style or want of style.

Some time before 1535 the Florence MS. was examined by the eminent Greek scholar, Janus Lascaris (1448?–1535). He was himself a Greek speaker and so saturated with the ancient form of the language that it was almost native to him. He prepared a transcription of the *De ossibus*, improving and "purifying" it linguistically. This version came into the hands of the humanist Ferdinando Balamio, the "Sicilian". He made a translation of it into Latin which he published at Rome in 1535. Balamio withheld the Greek version of Lascaris from Vesalius. The Greek text remained unknown until published in Paris in 1543 by Martin Grégoire and Jacques Dubois, the teacher of Vesalius. I have not seen this edition but it corresponds to the text printed by René Chartier in his great edition at Paris in 1679 and reprinted by C. G. Kühn at Leipzig in 1821. Since this goes back to Lascaris who, in his turn, depended on the Florentine MS., it is not likely that it will be much improved.

The following translation is from the reprint in Kühn's text. There is no later or more critical edition. Lascaris was not a medical man and some of his reconstructions of the Greek text might have been better done by one with more technical knowledge. Balamio, though a medical man, was no anatomist. My translation must be taken as a first attempt to render a corrupt text. Galen, it must be remembered, normally worked on apes and in some passages here, notably in the account of the sacrum, he is evidently still describing simian rather than human forms. Nevertheless there is no doubt, from many references in his other works, that he had access to human bones.

The text is of interest also as an early attempt to construct an anatomical nomenclature. This is a

very important and highly significant matter. To bring it out I have, in many cases, printed transliterations of Greek anatomical terms in heavy type. In this I have followed no regular rule but have had in mind the presentation of a translation which will indicate how our own anatomical nomenclature has arisen from a system that lacked its present exactness. The ancient anatomists—and indeed ancient men of science in general—lacked the inestimable advantage of a classical language on which to draw for technical terms. All the sciences continue to draw for their new technical terms on Greek and Latin. In this sense, these are still living languages.

Square brackets indicate my own additions or explanations; round brackets indicate that the enclosed words or their Greek equivalents are to be found in the text. I have transcribed Greek words into Latin letters, using heavy type so that they will catch the eye. I have indicated the pages of Kühn's Greek text by marginal numbers. The paragraphing is my own and is absent from the MSS. and from the printed text. The numbers in round brackets, (1), (2), etc., refer to the notes at the end of the paper.

p. 732 [*Proemium.*] I hold that the physician should know the individual character of each bone and how it is placed in relation to the others if he is to treat fractures and dislocations successfully. Obviously all medical treatment must aim at the "natural" (**cata physin**). One ignorant of this will not know how affected parts deviate from the normal (**physin**) or
p. 733 how to restore them. He could neither diagnose diseases nor treat them aright.

The bones are the hardest and driest parts of the living body and, as one might say, the "earthiest" (1). They underlie and support the rest, as do foundations. All else depends on or is attached to them. Some are large with extensive cavities, full of marrow, others small, solid, marrowless, and devoid of perceptible cavity. Most large bones have **epiphyses** (2) (lit. growths on) at both ends. Such is the humerus, with ulna and radius below it, and similarly femur, with tibia and fibula. The lower jaw has marrow but no epiphyses, but its lower end is united by **symphysis** [lit. growing together] while the upper end has two **apophyses** [lit. growths from], the **corōnē** (3) and the "neck". An **apophysis** differs from a **symphysis** in that the latter is the union of one bone with another, while the former is part of the bone itself.

p. 734 Perhaps I should now explain the other terms that I shall use here so that, when they occur, my meaning may be clear and the continuity of discourse unbroken. Since I prefer always to clarify any point as it arises, it is best to start now.

The whole linked system of bones of the human frame is named a **skeleton**, and some authors have given to books in which they discussed the bones the title *On the Skeleton*. Bones are joined in two different ways, by joint (**arthron**) and by **symphysis**. There are several sorts and kinds of each. A joint is a natural (**physicos**) connexion of bones; a symphysis a natural union of them. "Natural" (**physicos**) is added to each definition because displaced or dislocated parts are connected with one another, but not "naturally", and broken parts that have callused together are united but not "naturally".

p. 735 Hippocrates often calls the end of a bone attached to another a "joint" (**arthron**); not either end indiscriminately, but the rounded end that enters the hollow of the adjoining bone (3a). There are two kinds of joint, **diarthrōsis and synarthrōsis**. They differ in the amount of movement they permit. Diarthrosis is a conjunction (**syntaxis**) of bones which plainly move in relation to one another; synarthrosis is a union (**synthesis**) of bones the motion of which is not apparent or considerable, but indistinct and even difficult to discern. There are three kinds of **diarthrōsis**. Modern physicians call one **enarthrōsis** [that is ball and socket], a second **arthrōdia** [that is with surfaces only slightly concave and convex], and a third **ginglymoid** [hinged]. These names were not in use among the older physicians but verbs and adjectives formed from them can be found in their writings.

p. 736 It is perhaps right for clarity to coin words, deriving them from those already current. There is then an **enarthrōsis** when the receiving cavity has a fair depth and the head that enters it is pronounced, but an **arthrōdia** when the cavity is shallow and the head short. I call a head "pronounced" or "short" with reference to the neck on which it is set. "Necks" are narrow processes (**apophyses**) of the bones that terminate in a thicker and rounder end called the "head". When the process ends sharply it is no longer called "neck" but **corōnē**. A cavity receiving a head, if deep, is called a **cotylē**, if shallow, a **glēnē**. The third form of diarthrosis called **ginglymus** is when the connected bones fit each other, as with [certain]
p. 737 vertebræ, and with the **diarthrōsis** of ulna and humerus. But there is a difference here, too, for the apposition of the vertebræ is around a centre, whereas humerus and ulna hinge into each other (3b).

There are three kinds of **synarthrōsis**, suture (**raphē**), **gomphōsis**, and **harmonia**. With suture the elements are as though stitched together, as with the bones of the head (4). [Here eight omitted verbose lines enlarge on the equation suture=stitching=serration.] Harmonia
p. 738 [apposition] is articulation along a simple plane; certain bones of the upper jaw are thus related to one another and some of the bones of the cranial vault to these. **Gomphōsis**

[lit. nailing in] is articulation by infixation; it is an intermediate state and it approaches symphysis in that if a thing be firmly nailed in, no motion remains possible for it. So with the teeth, for their extraction or falling out prove that they are not fused with the sockets.

Having spoken of the other kinds of joints, I must discuss also **symphysis** (lit. growing together). It has two primary kinds, for some bones grow together of themselves, some by external aid, the former are more porous and soft, the latter more dry and thick. Uniting by these external means there are three species of symphysis for which there are no time-honoured terms, but if you seek names, you can call the symphysis by cartilage **synchrondrōsis**, that by tendon **(neuron) synneurosis**, and that by flesh **(sarcos) syssarcosis.**

p. 739 Since we have mentioned **neura**, it is well to distinguish them. Three kinds are described. Some are called "voluntary", and arise from the brain and spinal cord [= nerves]. Others are called "conjunctive" and derive from the bones [= ligaments]. The third kind is called **tenontai** and spring from muscles [= tendons]. To avoid obscurity from equivocal terms, I call all those which come from the brain and spinal cord, "voluntary **neura**", all from muscles, "**tenontai**", those from bones, "**syndesmoi**" (5). With this agreement about the use of words, we may discuss each bone separately, beginning with the **cranion**, for so they call the bone of the head.

Chapter 1.—I have said that on the head-bone, called **cranion**, are certain sutures. How many, of what nature, and how each appears, will now be set forth. First, their position
p. 740 and number varies with the nature and shape of the skull, whether oval, spherical, or acuminate. As to its nature; both anteriorly and posteriorly there is a prominence which presents three sutures, two transverse, of which one passes through the **inion** and the other through the **bregma**, and the third extends through the length of the head, from back to the front. The anterior suture is called **stephaniaia** (i.e. garlanded = "coronal"), since garlands are placed round the head there; that behind is called **lambdoid**, as shaped like the Greek letter **lambda**—Λ. The shape of these sutures, taken together, is likened to the Greek letter **ēta**—H. Thus are the sutures of the "natural" skull arranged.

p. 741 In the acuminate skull the posterior prominence is defective, as is also the lambdoid suture. When the anterior [prominence is defective], so is the coronal. In either case the shape of the remaining sutures is like the letter **tau**—T. If both prominences be defective, the two sutures preserved cut each other at right angles like the letter **chi**—X; the transverse [suture] is then roughly at the middle of the head; the other suture runs in the length, as in all crania, for this always remains the same though the others vary with the head-form.

Two other lines parallel to the longitudinal run forward from behind the ears. They are produced by two bones meeting one another, though not by suture like the former cases but, thinning gradually to a mere scale, the bone coming down from the bregma [parietal] is set under the bone running upwards from the ears [temporal]. Wherefore some do not call these merely "sutures", but "scale-like sutures" (**lepidoeidēs** = squamiform). Thus there
p. 742 are five sutures proper to the vault of the cranium, lambdoid, coronal, straight [sagittal] and, parallel thereto, two scale-like.

There are also two [sutures] common to the upper jaw-bones and to the **[sphenoid]** bone between the two, which latter bone some assign to the **cranion**, others to the upper jaw. The appearance, size, and relations [of this **sphenoid** bone] I now explain.

The lower ends of the sides of the **lambdoid** sutures extend to the base of the skull. They pass down between the petrous **(lithoid)** bones and the **diarthrōsis** with the first vertebra. Here a short transverse line joins them [occipito-sphenoid suture]. Note the line of which
p. 743 I have spoken, common to the vault and to this bone [i.e. to sphenoid] for, running up on either side to the hollows in the temples, it reaches the end of the coronal suture; then, turning round again, it reaches the palate, running to the back teeth. Thus this suture embraces the bone which resembles a wedge **(sphēn** hence **sphēnoid)** between the vault of the skull and the upper jaw (6). The part of the suture that runs up to the coronal pertains to the vault, while that which descends to the palate forms the boundary between the **sphēnoid** bone with the upper jaw. Let it be called **sphēnoid** for clearness. To this bone on either side are wing-like **(pterygoid)** outgrowths **(apophyses)** with hollows.

The other suture of the skull which forms the boundary [of the **sphēnoid**] with the upper jaw starts from the hollows at the temples where the suture common to vault and sphenoid meets with the end of the coronal suture. It goes forward from there to the orbit and, passing through its midst, engages **(synaptei)** with the **mesophryon** [i.e. orbital part of frontals] (7).

p. 744 There are thus in all six bones in the vault apart from the sphenoid, two at the **bregma** with a common straight longitudinal suture [parietals]; another two below these, one at each ear [squamosal part of temporals]; a fifth at the **inion** [occipital]; and the sixth is the frontal **(metōpon** = "between the eyes") (8). The bones at the bregma [parietals] are bounded behind by the sides of the **lambdoid** suture, in front by the coronal, below by the squamiform sutures, above by the straight [sagittal] suture running lengthways.

The bones next to the ears [temporals] are limited above by the squamiform sutures,

behind by the prolongations of the sides of the **lambdoid** suture, in front by the suture between **cranion** and **sphēnoid**. The bones of the **bregma** [parietals] are four-sided, but those just mentioned [i.e. temporals] are three-sided. The fifth bone of the vault (**cranion**), that at the **inion** [occipital] is limited by the lambdoid suture with its prolongations and by the sutures that we said joined them. It contains within itself the largest of the foramina of the skull
p. 745 [foramen magnum], that next the first vertebra. The remaining bone, that at the **metōpon** [frontal], is circumscribed by the coronal suture and the suture with the upper jaw. Of the bones [of the vault], those at the **bregma** are the most porous and weak, that at the **inion** the thickest and strongest, and that in the forehead intermediate.

Of the other bones those of the ear [temporal] are composite, for one part is called "stony" (**lithoeides** = petrous), and so indeed it is. It is bounded by the divergent ends of the **lambda**-like suture. In it also is the **styloid apophysis** which I call "needle-like" or "pen-like", and the outgrowth (**ecphysis**) surrounding the auditory meatus (**acousticon poron**). Parts of it are firstly the **ecphysis** called **mastoid** [= "breast-like"], secondly the **zygōma**, and thirdly the part below the temple. As to the foramina of the skull I shall speak of them in dealing with the anatomy of the vessels and nerves, for they have been created for them (9), for
p. 746 there passes through each either an artery, a vein, or a nerve, or some or all of these.

Chapter 2.—Outside the temporal muscle is set a bone having an oblique suture in its midst. Its back part joins with the **cranion** at the ear, its front part with the edge of the optic rim (**peras ophryos**) at the small [i.e. narrow] **canthos** (10) of the eye. The whole bone is called **zygōma**.

Chapter 3.—The sutures marking off the upper jaw from vault (**cranion**) and **sphēnoid** have been distinguished. Now I shall speak of those in the jaw itself, but it is best to deal first with the word "suture" (**raphē**) and to explain how all the more modern anatomists employ it. They call even union by apposition (**harmonia**) a "suture" (**raphē**). This is not surprising for you cannot find the saw-like combination of bones equally perfect in all the
p. 747 sutures of every skull. With the same arrangement of bones, in one skull there may be an interdigitation (**syntaxis**), in another mere apposition (**harmonia**). Moreover on disarticulating such [apposed] bones I have sometimes found them fitting into each other underneath, like a stitching rather than an apposition. Therefore one need not hesitate to call them all "sutures".

Consider first the suture beneath the [temporal] process of the **zygōma**. The part running back ends in the hollow in the temples, below which is the **zygōma** itself. There it reaches the suture with the sphenoid. The other [part of the **zygōma**] runs first direct and then upward to the orbit, extending to the middle of its lower rim. Anteriorly [the **zygōma**] branches into three. The first passes by the greater **canthos** (10) toward the **mesophryon**. The second extends through the cavity under the same canthos toward the suture with the **cranion** so that the canthos itself and the foramen beneath it (i.e. orbital fissure), which is
p. 748 the largest in that region, is embraced by the said two sutures. The third part of the said division [of the **zygōma**] extending downward from the lower rim of the orbit, unites deeply by suture [with the bone of upper jaw] (11).

On either side there are three bones of the upper jaw, whereby it is linked to the **cranion**. The largest is that of the **zygōma**, which is attached to the temple and to the brow and also embraces the orbit and the lesser **canthos** extending to the so-called **mēlon** [cheek bone, i.e. process of maxilla]. Next to it in position and size is the bone in the orbit itself [i.e. orbital process of palatine] which embraces the nerve to the upper jaw [i.e. maxillary nerve]. Smallest of all is the bone round the large **canthos** [i.e. lacrimal]. Some anatomical writers maintain that these three bones are one [with the maxilla], either ignorant of the two sutures that cleave the depth of the orbit or else deliberately omitting them, because of their smallness.

p. 749 Under all these there is a considerable bone [i.e. the maxilla] on each side, and set under the three already mentioned. The so-called **mēlon** [cheek-bone, i.e. malar process of maxilla] is part of it. This [maxillary] bone has the sockets of all the teeth except the incisors. Four sutures define it; above is the suture that runs up between zygomatic bone and **mesophryon**; below is the straight suture [intermaxillary] in the middle of the palate; and the two remaining [sutures] unite these. Of them one starts from the **mesophryon** and runs along the nose and comes out between the so-called "canine" tooth and the incisors; the other, having had a part in common with the [orbital surface of the wing of the] **sphēnoid**, runs in a wide curve independently to the back tooth, until it joins with the straight suture in the roof of the mouth.

Beside these two very large [maxillary] bones lie two small bones [palatines] through which there runs the perforation from the nose to the palate [posterior nares]. Their boundaries are their own portion of the aforesaid suture [with the maxilla], a suture at right angles to the sphenoid bone, and [a suture] between the back teeth. These sutures divide them from
p. 750 the surrounding bones and they are marked off from one another by the straight suture in the roof of the mouth.

Chapter 4.—There are two bones in the nose, limited by sutures from the **mesophryon**, which I detailed as third of the large bones [of the cranial vault]. There is also a third suture in the nose itself, between the nasal bones, which starts from the mesophryon and runs straight through the nose. The lower ends of these bones have outgrowths of delicate cartilage called *alæ* (**pterygia**).

There remains a bone, containing the roots and sockets of the incisors [= premaxilla], at the end of the jaw. This usually seems undivided because of the perfect fitting together of the bones forming it, but sometimes in well-dried skeletons the suture is seen stretching right across the palate.

p. 751 Thus there is some basis for the dispute as to the number of bones in the upper jaw. Some indeed reckon them not as six but as two, omitting the bones within the orbits as too small. Some assign the posterior openings of the nose to the large [maxillary] bones. And some again separate them [i.e. the maxillæ] from those [i.e. the palatines] but make a single bone of the two [maxillæ]. Moreover the end of the jaw, as I have said, is held by some to be single and by others to be of two bones. More important than all these vagaries is that among the bones of the upper jaw very many reckon the **sphēnoid**.

If one wished to make the bones [in the skull] as numerous as possible, there would be fifteen, but if one wished the opposite there would be but eight. I shall enumerate them [first] as fifteen.

First there are the six bounded by the sutures of the **cranion** and that from the temples under the zygoma and in the lower part of the orbit [2 frontals + 2 parietals + 2 temporals] to the **mesophryon**. Next are the two large bones [maxillæ] to which the **mēla** [i.e. malar
p. 752 processes] and almost all the teeth are attached. And then there are two others at the openings of the nose [palatines]. Then there are the two of the nose itself [nasals]. Then there are the other two at the end of the jaw in which the incisors are set [premaxillæ]. And beyond all these is the sphenoid which alone among them is unpaired.

Again the skull (12) may be divided into eight bones thus: The six as above are counted as two. The bone at the end of the jaw [premaxilla] as one and that at the opening of the nose as one [palatine]. There are two peculiar to the nose itself [nasals], and another two are the largest of the bones in the jaw which include the **mēla** and almost all the teeth [maxilla] (13).

Chapter 5.—The teeth must be reckoned among the bones though some theorists deny it. If they will not allow this, they must give them some other designation. Obviously they
p. 753 cannot be called cartilages, arteries, veins, or nerves, much less fat, hair, flesh, glands, or any other of the bodily parts. Were I to omit them both in the anatomy of these parts and in that of the bones, on which I am now embarked, I should not speak of them at all. Let us then bid farewell to these theorists.

There are sixteen teeth in each jaw. Four in front are called "cutters" (**tomeis** incisors) which all have a single root. Next on each side are the dog-teeth (**kynodontes** lit. dog-teeth = canines) also with a single root. Next are the grinders (**gomphioi**), five on each side. The grinders in the upper jaw have three roots, those in the lower two, though often some of the upper are found with four roots and some of the lower with three, and specially the first two among them all on the inside and more rarely the third. In some cases there are not five grinders on each side but four or six. They are not only called "grinders" (**gomphioi**) but
p. 754 also "molars" (**mylai** in the feminine gender). They get this name, I think, by **metaphor**, for with them we grind and triturate "cereals" as do mills (**myloi** in the masculine gender) the fruits of Ceres (**Dēmētēr**) (14). The canines which are very like those of a dog, get their name therefrom, and the incisors (**tomeis**) because they cut (**temnein**) as with a knife all cuttable food. This is true, of course, of soft foods for which Nature designed them, just as canine teeth were for hard foods, not to cut but to crush. All are fastened in the sockets (**bothria**) of the **phatnia** (alveoli). The **phatnia** are the surrounding bones, the **bothria** are the hollows in which the teeth are set. Teeth alone among the bones share in the soft nerves from the brain, and hence they alone are obviously endowed with sensation.

Chapter 6.—The bone of the lower jaw is not single, as one might think for, when boiled, it, too, is separated at the point of the chin, so that it is seen to be composite (15). The part
p. 755 that extends upward to the head ends in two processes. The sharper receives the tendon running down from the temporal muscle, while the other diarthroses with the skull under the **mastoid** (= breast-like) process (16). A rounded **condyloid** surface fits into the **glēnoid** cavity there.

Chapter 7.—In the whole spinal column there are twenty-four vertebræ (**spondyloi**). Either more or less than this number is as unnatural as are acuminate skulls. The vertebral system is divided into neck, back, and loins, and os sacrum (**hieron osteon**) (17). The neck is joined to the skull. The dorsal [vertebræ] which come next extend throughout the **thōrax**. The remaining part below is called loins (**osphys**). At its end it has the so-called "sacred bone" (**hieron osteon** = os sacrum) which some call the "broad bone". The vertebræ in the neck number seven, in the back twelve, in the loins five.

p. 756 *Chapter* 8.—Of the neck vertebræ the first two form complete **diarthrōses.** Of the other five the foreparts are bound together by strong ligament. It is not by cartilage that they are united—as some think—but by the membrane that covers the two **meninges** of the spinal marrow insinuating itself into the space between [every] pair [of vertebræ] and binding them together. So with all the vertebræ except the two first, as I shall explain.

The head moves in two ways, nodding and rotating. The former is determined by the **apophysis** of the second vertebra **[odontoid]** which is like a fruit-stone **(pyrēnoid)**—the latter by the diarthrosis of the first [vertebra] with the condyles **(corōna)** on the skull. These [diarthroses] are between the side parts [i.e. transverse processes] of the first vertebra and the skull itself.

p. 757 The **pyrēnoid apophysis** runs straight up from the front part of the second vertebra and is fastened to the skull by a strong and round [apical] ligament, the first vertebra providing a suitable space wherein it is securely held with a ligament at right angles, produced from the first vertebra [i.e. transverse lig. of atlas], laid on it. Some call this [process] the **odontoid** (i.e. tooth-like) **apophysis** and from it Hippocrates named the second vertebra from a tooth **(odous,** stem **odont-)** (18). The first vertebra has other two **glenoid** cavities on its lower surface, like those in the upper. The upper are naturally larger, since they articulate with the skull; the lower articulate with the second vertebra. The first vertebra is very broad and slender; the next is narrower, yet stronger, as are all the other vertebræ after it. In proportion as the cord becomes narrower, consumed by the outgoings **(apophyses)** of the nerves, the breadth

p. 758 of the lower vertebræ diminishes, each being proportional (19) in thickness to that of the cord which it surrounds.

All [other] vertebræ have **apophyses** at the sides which run up and down, whereby they articulate with one another. Of their other characteristics most are shared, but some are not and of these I shall speak next. All have posterior **apophyses** called "spinous processes" except the first vertebra. This [first vertebra] alone has an anterior apophysis, and it is a small one. Again only the vertebræ of the neck have foramina in the lateral apophyses, except the seventh, which is also the last, which you rarely find perforated. The vertebræ in the neck have these apophyses also slightly cleft, except the first two [the lateral apophyses of] which are single. The sixth has apophyses that are obviously double and are the largest of them all, just as the vertebra itself is the largest. The inner of [the processes] is fairly

p. 759 broad. The anterior part of each, by which they are united with one another, is elongated, particularly in the cervical vertebræ, except the first. To the nerves issuing from the cord and emerging at the junctions of the vertebræ, each cervical vertebra contributes about equally with the first. Of the others those that lie higher contribute in general more.

Chapter 9.—I have said that the vertebræ of the **thōrax** are twelve. Rarely one more or less may be found, oftener less than more. In these vertebræ the spinous processes increase to the tenth. The transverse processes are large for, by them, the vertebræ articulate with the ribs. The body of the first [thoracic] vertebra is a little compressed below, but in the vertebræ which follow this gradually ceases. Their spines, as far as the tenth [dorsal] vertebra,

p. 760 are much like those of the cervical, sloping downward but from the tenth they begin to slope the other way, in the tenth indistinctly, but more plainly in the others. So, too, with the transverse processes, for those above the tenth slope downward, those following it upward. Those of the tenth only incline neither way. For this is the only vertebra to have not only its upward **apophyses** but also its downward terminating in **condyloid** ends, just as the first cervical vertebra has both **glēnoid**, and those below the tenth the reverse.

Chapter 10.—Nearly enough has already been said about the lumbar vertebræ, namely that they are five, that they are the largest and thickest of all, while their cavity is narrow,

p. 761 as is the cord in them (20) but I shall mention here such [other] peculiarities as they have. In the inner part of each of the lumbar vertebræ veins penetrate through distinct, numerous, and irregular foramina. Of such in other vertebræ you can see few if any and those quite small. Moreover there is [in the lumbar vertebræ] a large downward-tending **apophysis** where the nerves emerge. Sometimes it is found in them all, but sometimes it is small or absent in the last vertebra. The [lumbar] vertebræ above always have it, as do the last two thoracic.

Chapter 11.—The os sacrum resembles the vertebræ in that it articulates with the vertebra

p. 762 above, for it receives downward processes from it as it in turn receives those of the vertebra above. It has a spinous process like the others. Its lateral processes, however, are large and broad, and their outer parts **have a glēnoid** hollow to which is attached the "hollow-bone" [innominate]. The sacrum is composed of three parts, intrinsic vertebræ, as it were, of its own (21), at the end of which lies a fourth, another bone, called **coccyx.** When they are all cleaned by boiling, the structure [of the sacrum] is seen to be the same as that of the vertebræ. The nerves from the spinal cord, issuing through its foramina, pass out of its would-be "vertebræ", just as they do along the spinal column as a whole, yet not from the sides but internally and externally. There are three pairs of them.

Chapter 12.—At the end of the "broad bone" [sacrum] is the **coccyx**, which also is of three parts. They are rather more cartilaginous than those of the "broad bone", particularly that
p. 763 at the end. Nerves pass through their junctions from back and front, the first pair where the coccyx adjoins the "broad bone", the second at the junction of the first and second, and the third at the junction of second and third. What remains of the spinal cord passes through at the end of the third and it alone is unpaired.

Chapter 13.—The **sternon**, ribs **[pleurai]**, and dorsal vertebræ form the bony **thōrax**. Twelve ribs on each side correspond to the vertebræ. Each of the seven [true] ribs forms a **diarthrōsis** with one vertebra and a **synarthrosis** with parts of the **sternon**, from the lower end of which a triangular [ensiform] cartilage extends. The **diarthrōsis** of each vertebra with a rib is thus: the beginning of the rib is attached to the root of the fransverse process at a
p. 764 **condyloid** prominence; the hollow receiving it is superficial and small and both hollow and beginning of the rib incline somewhat upward. Next the rib rests on the transverse process and at the end of it has another **diarthrōsis** tending downward. Thus the rib has a double articulation with the vertebra. That with the **sternon** is less clearly visible; but is not obscure if you remove the surrounding ligaments, for the cartilaginous ends of all the ribs have **condyloid** heads forming **diarthrōses** with the bones in the **sternon**, each of which has a hollow on the surface. These joints, however, permit only limited movement, so that they are almost **synathrōses**. In many other parts of the body there are bony junctions which are betwixt and between, so that we are in doubt whether we should call the articulation movable or immovable.

The **sternon** as a whole is like a sword, hence some call it the **xiphoid** [ensiform] bone;
p. 765 nevertheless some give this name not to the whole [bone] but only to the cartilage at its end.

The shape of the ribs is by no means simple. On leaving the vertebræ, they run anteroinferiorly and after some distance suddenly bend back upward toward the sternum. As they turn, they cease to be bone and become cartilage. The remaining five ribs, called "false" **(nothai)**, form a union **(symphysis)** with the **diaphragma** and with each other, terminating in fine cartilage. Only the last is free at its end and really "false" **(nothē)**. The ribs have not all the same length, the upper and lower being shorter, those in the middle longer.

Chapter 14.—The **ōmoplatai** (22) [scapulæ] lie behind the **thōrax**. They are united by muscles with the **inion** of the skull, the spinous processes of the vertebræ, the ribs, and the
p. 766 front of the **larynx**. They are very asymmetrical **(anōmaloi)** and irregular **(anomoiai)** in all their parts, for they are convex without, concave within, their base delicate and elongated below, their apex hard and narrow. They have cartilages joined to many of their parts, especially at the base.

Starting thence low and small on the spine it increases to the level of the top of the shoulder **(acrōmion)** where it is joined by **diarthrōsis** (22a) to the clavicle **(cleis)** (23). Some anatomists call this combination **acrōmion**, but others maintain that besides these two conjoined bones there is here a third bone, found only in man, which they call **catacleis** or **acrōmion** (24). The tract **(apophysis)** below this on the scapula is called the "neck of the scapula". It ends in a **cotylē** with which the head of the humerus forms a **diarthrōsis**. There is a small pointed **apophysis** here within, called by some anchor-like **(ancyroid)**, by others **coracoid**, with its
p. 767 end bent like a **corōnē** (24a).

Chapter 15.—Each clavicle **diarthrōses** with the upper end of the **sternon**. The clavicle is porous and its form and thickness change [in its length]. Its lower part which diarthroses with the **sternon** is thicker and rounder than the other. The part next it is much thinner but round. All following is irregular until the junction with the scapula, where it flattens out. The mid-part curves outwards as it approaches the scapula.

Chapter 16.—The humerus—the largest bone except the femur—diarthroses at both ends. At the shoulder end it has an **epiphysis** which swells into a head on a smaller neck. And there is a broad incised hollow in the front [= anatomical neck], dividing the whole head into two as though [both were] **condyles**. The lower end divides into unequal condyles. The
p. 768 radius diarthroses with the outer, but no bone engages the inner, so that it seems much larger than the outer, though it is but little larger.

In the lower end of the humerus is a fossa like those by the **trochlea** round which the ulna turns. At the edge of this [radial fossa] is another fossa, both front and back, the former being smaller. These [fossæ] receive the **corōnai** of the ulna, the anterior when it is flexed frontward, the posterior when extended backward. Elsewhere the humerus is bowed, yet not sharply or uniformly but convex anteriorly and outwardly, and concave in the reverse.

Chapter 17.—The name **pēchys** (forearm) is given to the whole part between humerus and **carpos**, and also to the larger bone [ulna] set therein under the other, called "radius" **(cercis)**.
p. 769 At its upper end this [radius] embraces the outer condyle of the humerus with a shallow

cavity. The function of this articulation is to bring round the arm from the prone to the supine position. The **pēchys** (ulna) has two **corōnai**, the smaller in front, the larger behind. They comprise its **sigmoid** (25) notch on which is inserted the **trochlear** surface of the humerus between its **condyles**. The function of this articulation is to extend and flex the whole forearm. The **pēchys** (ulna) is bound to the **cercis** (radius) with comparably strong ligaments at either end, but in the middle they remain separate. Each has an **epiphysis** at the **carpos**, which [junction] is convex without [i.e. peripherally] and hollow within [i.e. proximally], the ulna corresponding to the little finger, the radius to the thumb. The **carpos** moves on this cavity and **diarthrōses** with it. Prominent is the **apophysis** called **styloid**. It articulates with the
p. 770 **carpos** but its function is to permit the wrist to move laterally while the companion **apophysis** is responsible for direct movements by which the hand is extended and flexed.

Chapter 18.—Eight bones in two rows form the **carpos**. All are hard, small, marrowless, and irregular. They are in places convex, concave, straight, rounded, and all bound together by fibro-cartilaginous bonds. They are **synarthrōsed** to each other but do not, as some think, grow into each other. The carpos is slightly convex outwardly [i.e. on the extensor surface], concave inwardly. The upper portion of the **carpos** consists of three bones, rounded and **diarthrōsed** to ulna, radius and **styloid**, except that the **carpos** by the little finger [triquetral] encloses the **styloid** in a little **glēnoid** hollow [of its own]. The middle bone [= lunate] occupies that region where ulna and radius meet. The third [scaphoid], which is twofold,
p. 771 is embraced by the radius. The lower portion of the **carpos** is **synarthrōsed** to the **metacarpos** through its four bones. The fifth [metacarpal] bone is in that part of the carpos where lies the **styloid apophysis** of the ulna (26).

Chapter 19.—The part between **carpos** and fingers is called the **metacarpos**. It is **synarthrōsed** to the **carpos** but **diarthrōsed** to the first **phalanges**, a name given to the finger-bones. Only the thumb has its first **phalanx diarthrōsed** to the **metacarpos** at the side. Of the fingers, each is formed of three bones, the end of each **phalanx** fitting into the cavity placed at the beginning of the next. It seems reasonable to say that the thumb too is made up of three bones and not to add a first metacarpal to it, for it has a **diarthrōsis** at both ends, as with the phalanges but not as with the metacarpals. Thus some would reckon the metacarpals
p. 772 as four, and the bones of the five fingers as fifteen. Alternatively some reckon fourteen phalanges and five metacarpals.

Chapter 20.—With the large, straight, lateral outgrowths of the sacrum are associated two bones "which have no name" [Latin *innominata*]. Their broad upper parts are called "bones of the flanks" [ilia], the lower and outer parts after the entrance [of the femora] **ischia**, and the parts that run up from there to the front, which are delicate, fenestrated, and grown together at the end, are the "pubes" (**ostea hēbēs** lit = bones of puberty). There is a very large **cotylē** in each **ischion**, united with the head of the femur by a very strong ligament.

p. 773 *Chapter* 21.—The femur, the largest bone in the body, is diarthrosed above to the **ischion**, below to the tibia. Above it has an **epiphysis**, a spherical head on an oblique neck. Below, expanding gradually, it ends in two **condyles** which are so large that they may well be called "heads". It is bound to the leg not only by membranous ligaments surrounding the whole joint, but also by three others at once strong and rounded, of which the first extends along the outer part of the articulation, the second along the inner, and the third between the posterior and inner parts. The femur is convex anteriorly and externally. It has two **apophyses** below the neck called **trochanters**, the outer being much larger and called the **gloutos** (26a).

p. 774 *Chapter* 22.—The name **cnēmē** is given to the limb between knee and **astragalus** but also to the larger bone therein. This [tibia] is on the inner side and the femur diarthroses only with it. The outer bone is called **peronē**. It is much more slender than the tibia, nor in its length does it reach the knee. It is **synarthrōsed** to the tibia at both its ends but in the mid-parts completely separate. The tibia, where it joins the femur, has a large **epiphysis** that receives the femur which enters two hollows of the tibia. Between the hollows a fibro-cartilaginous prominence enters the deep cleft between the condyles. The fleshless and thin front part of the tibia is called **anticnemion** (shin). The ends of the tibia and fibula on either side are called the "hammers" (**sphyra**, Latin *malleoli* = little hammers). These convex, fleshless, and projecting parts are popularly but quite mistakenly called **astragaloi**, for the **astragalos**
p. 775 is enclosed by these hammers, sheltered by them on all sides, and inaccessible. But the hammers are the **apophyses** of the tibia and fibula respectively, convex on the outside, visible on the surface, and [forming a] hollow within.

Chapter 23.—Outside the articulation of femur and tibia lies a cartilaginous circular bone, enclosing in well-fitting cavities the convex and condyloid parts of the bone beneath, and filling the space between femur and tibia with a blunt prominence. Some call this bone "knee-cap" (**epigonatis**), others the "millstone" (**mylē** = patella).

Chapter 24.—The aforementioned lower **apophyses** of tibia and fibula enclose the **astragalos**. Its so-called "chariot" **(tetraoros)** is tilted upwards (27). Of its other parts those
p. 776 at the back are smooth and moderately rounded, with an upward tilt; those in front articulate with the bone called **scaphoid** [boat-shaped = Latin *navicularis*] by a spherical head on a longish neck. On either side it ends between beetling prominences [malleoli], enclosed by the smooth cavity under the tibia and fibula. Under it lies the largest bone in the foot, called **pterna** (calcaneum), enclosing the rounded parts of the **astragalos** and fitting two projections into suitable cavities. The part on which we tread is gently rounded and flat. It is rounded also at the back, and projects beyond the straight line of the tibia. Of its front parts, that on the side of the great toe is set under the head of the **astragalos** and has no bony attachment, that on the side of the little toe **synarthrōses** with a bone called "**cuboid**". On the outside it
p. 777 is beside the **scaphoid**, but the latter is hollow where it articulates with the **astragalos**, whereas the **cuboid** bone is convex. Next come three little bones (cuneiforms), **diarthrōsing** with the lower end of the **scaphoid**. The **cuboid** also adjoins them on the outside. And with these four the **tarsos** is complete.

Chapter 25.—Here begins what is called the **[metatarsos] pedion**. It is formed of five bones, next to which lie the toes, all of three **phalanges** as with the fingers, except the big toe, which alone has but two. Their joints are bound together by membranous ligaments, those in the astragalus and heel by very strong ones, and some of them are both round and fibro-cartilaginous.

It seems to me that this is all beginners need know about bones and the construction of the skeleton, and that there is no need to discuss now any small bone found in other parts, as in the heart, larynx and nose, and in some of the digits which are called **sesamoids,** or anything else of the kind.

NOTES

(1) *Earthiest* (**geōdestata**) must not be read here in its modern sense but in reference to the ancient theory of the four elements, earth, air, fire, and water, of which all matter was held to be composed.

(2) The term **epiphyses**, like the other technical terms in this work, must not be given the exact meaning ascribed to it by modern anatomists. *De ossibus* lies at the dawn of our anatomical nomenclature and Galen is inventing his own anatomical vocabulary. For this the Greek language was and is peculiarly apt, for it is, of its nature, insistently colloquial.

(3) **Corōnē** is frequently used by Galen, notably for the **coronoid** process of the mandible. It does not refer to the likeness to a crown but to the end of the shaft of a plough, as is made clear by Galen's contemporary, Julius Pollux in his *Onomastichon* I, 252.

(3a) The Hippocratic works do, in fact, in several places use **arthron** in the sense of the "ball" of a ball-and-socket joint.

(3b) In this paragraph Galen displays well the nomenclatory method which has made him the father o anatomical terminology.

(4) The Latin *suo*, I sew, is the root of our word *sew*, *sutor* a cobbler, *sutura* a seam, a stitching. Suture is used to translate Greek **raphē** which is from **raptein,** primarily to arrange words in order (hence *rhapsody*) and only later "to stitch".

(5) **Syndesmoi** are effectively our ligaments. Galen's use of the word **neuron** for three different kinds of structure has caused endless misunderstanding. He himself was aware of their distinctness, as this passage shows.

(6) The sphenoid bone does not seem to us wedge-like but the ancients included with it the cribriform plate of the ethmoid. When thus combined and looked at from above it justifies its title.

(7) The **mesophryon** is the mass of thick bone containing the frontal sinuses which projects above and between the orbits. It is a useful term for which we have, perhaps, no modern equivalent.

(8) Galen here treats the frontals as one united bone, as did Aristotle before him. Later in this book Galen reckons two frontals.

(9) Galen is always intensely teleological in his views. He says repeatedly in his works that parts and organs were "created" for this or that purpose. His scientific outlook is coloured by this view.

(10) Galen speaks of the small (narrow) and great canthus where we speak of the outer and inner.

(11) There may be a small lacuna in the text here.

(12) I have used the word *skull* here where the text, by some scribal error, says "all the bones above the jaw".

(13) Text here inserts a phrase which makes nine bones instead of eight. This seems to me a case of dittography and I omit it.

(14) By a lucky chance, by substituting the Latin goddess Ceres for the Greek goddess Demeter, the Greek word-play can be nearly preserved in English.

(15) That the mandible is here described as divisible shows that Galen was describing the mandible of an ape or, more probably, that the text is here corrupt since the human mandible is one of the most distinctive and accessible bones.

(16) By **mastoid** Galen cannot here mean the process that we call by that name, which is an inch behind the mandibular joint. I think that he means the nipple-like post-glenoid tubercle of the temporal bone.

(17) *Os sacrum*, sacred bone, translates **hieron osteon,** in which the sense **hieron** has often been said to be not sacred but big or solid. This has no classical authority and the origin of the term remains a mystery. *Os sacrum* appears first in the Latin work of Cœlius Aurelianus, probably of the fourth century A.D., and itself translated from a lost Greek work by Soranos.

(18) The reference is to *Epidemics* II, 2, 24, Littré V, 96.

(19) Proportional. Greek text says "equal".

(20) Six repetitive lines here omitted.

(21) In most apes accessible to Galen there are three sacral vertebræ. In the *De usu partium* XII, Ch. 12, he describes the sacrum as of four vertebræ. In fact the human sacrum has five, though sacra of four are not extremely rare.

(22) French has retained this term as *omoplate*.

(22a) Text says **synarthrosis** by error for **diarthrosis.**

(23) *Clavicula* diminutive of *clavis* = key = **cleis** seems a poor description of the bone. **Cleis,** however, primarily a bar or bolt, goes right back to Homer in the sense of collar-bone and is so used by Aristotle and Hippocrates. The **cleis** or clavis was, however, also a curved rod for trundling a hoop or a lever for turning a press. Either this or some early form of key must be the origin of the term.

(24) **Acromion,** lit. top of shoulder. The discovery that it is a separate ossification is ascribed by Rufus (*c.* A.D. 110) *De apellatione partium* to one Eudemos. The two centres by which the acromion ossifies unite with the scapular spine about the age of 16. It is untrue that they are peculiar to man.

(24a) The word **coracoid** is one of the puzzles of anatomical nomenclature. **Corax** is Greek for crow and **coracoid** can mean only "like a **corax**" and not "like the beak of a **corax**". Yet outside anatomy **corax** means also a hook, specially of a door-handle. It may be that this latter usage is from a root different from the other and that the meaning of **coracoid** comes near to that of **corōnē** as given in note (3).

(25) The reference is to the capital Greek **sigma** which is shaped like our C.

(26) In Galen's reckoning there are only four metacarpals, that of the thumb counting as a phalanx.

(26a) Hence our "gluteals".

(27) **Tetraoros,** four-horse chariot, is a term for the upper part of the astragalus, as used by Rufus *De ossibus* 38. If the bone be looked at from the medial aspect its trochlear surface resembles the body of a well-known form of chariot.

Section of Otology

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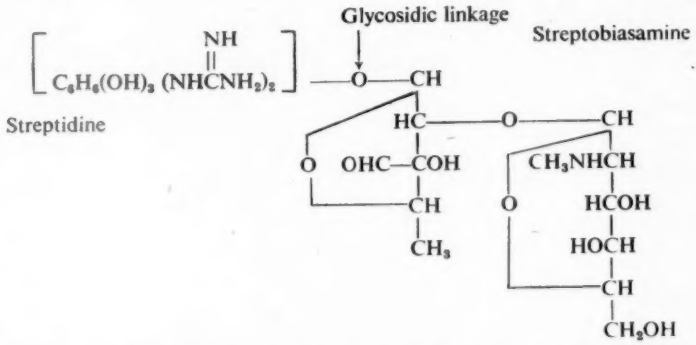
DISCUSSION ON THE TOXIC EFFECTS OF STREPTOMYCIN AND DIHYDROSTREPTOMYCIN ON THE ACOUSTIC AND VESTIBULAR SYSTEMS [*Abstract*]

Professor J. M. Robson and Dr. Roy Goulding: *Streptomycin and Dihydrostreptomycin.*

Structurally, streptomycin may be represented by the formula below:



It is thus an organic nitrogenous compound, comprised of a hydroxylated base, streptidine, joined by a glycosidic linkage to a nitrogenous disaccharide, streptobiasamine. The hydrochloride forms a crystalline double salt with calcium chloride and this is the usual form now dispensed. (Streptomycin et Calcii Chloridum, B.P.)

By the reduction of streptomycin at its free carbonyl group, dihydrostreptomycin is prepared.

The Activity of Streptomycin and Dihydrostreptomycin Against Micro-organisms

Streptomycin exerts an action against a large number of micro-organisms, both Gram positive and Gram negative. It is outstanding, however, in its effect upon *Mycobacterium tuberculosis*. Investigations directed towards a comparison of streptomycin and its dihydro-derivative have shown that:

Firstly, under controlled conditions *in vitro*, the minimal concentrations at which the two drugs inhibit bacterial activity are virtually identical for a number of organisms. This certainly applies to *M. tuberculosis* (Donovick and Rake, 1947; Edison *et al.*, 1948).

Secondly, *in vivo*, both drugs are equally capable of prolonging the survival time of animals experimentally infected with *M. tuberculosis*, whether of human (H37Rv), bovine or avian strains (Rake *et al.*, 1948; Edison *et al.*, 1948; Feldman *et al.*, 1948).

Thirdly, in the treatment of human tuberculosis, the results with dihydrostreptomycin, at least by empirical assessment, are comparable with those obtained by the parent drug.

Finally, bacterial resistance to the two drugs may be regarded as parallel (Edison *et al.*, 1948).

Mode of Action

The precise mechanism by which streptomycin compounds bring about their anti-bacterial effect, though of considerable interest, is as yet beyond our understanding. Reviewing the bizarre data available from studies of bacterial metabolism, Florey *et al.* (1949) concluded that "in the case of sensitive strains, streptomycin interfered with some essential metabolite or metabolic process".

Absorption and Fate in the Body

Unlike penicillin, streptomycin given by mouth is not inactivated in the gut. Nevertheless it is poorly absorbed, if at all, from the alimentary tract, neither is it taken up from the lungs when exhibited as an aerosol (Florey *et al.*, 1949).

Marshall (1948), estimating streptomycin levels by a chemical as well as a calibrated antibacterial technique, concluded that:

After intravenous injection the maximum serum concentration is recorded within a few minutes.

After intramuscular injection the maximum serum concentration is recorded within one or two hours.

The maximum concentration attained after intramuscular injection is similar to that prevailing at the same interval of time after intravenous injection.

In the dog, nearly all of the drug injected is excreted in the urine but in man this is not consistently so.

Distribution of the drug in a percentage of body weight approximates to its distribution in the extracellular fluid.

Renal plasma clearances for streptomycin in both dog and man are less than the reported values for glomerular clearance so, unless there is any binding by plasma proteins, excretion is by glomerular filtration alone.

After the introduction of streptomycin by the intramuscular route, appreciable quantities may be detected in most of the body fluids, including those of the eyes. There is also transportation across the placental barrier into the fœtal circulation. By contrast, a negligible amount enters the red blood cells, thick-walled abscesses or large tuberculous cavities and comparatively little reaches the cerebrospinal fluid, except in the presence of acute meningitis. On the other hand, streptomycin may be given by the intrathecal route, when it is retained in the subarachnoid space for up to thirty hours (Florey *et al.*, 1949). Systemic dispersion from this site is then of a very low order.

Levin and his colleagues (Levin *et al.*, 1948), using for dihydrostreptomycin a modified cup-plate method of assay with *Staph. aureus*, found that its absorption, distribution and excretion followed the same pattern as streptomycin. They went on to deduce that any difference in behaviour of the two substances, therapeutically or toxicologically, must be attributed, not to variations in their concentrations in the body fluids but to other, probably intrinsic, factors.

Toxicity

Acute.—In themselves, figures for the lethal doses of streptomycin and dihydrostreptomycin are of little importance. However, as a basis of comparison between the two compounds, the following figures for the LD 50 in the case of mice are informative:

Streptomycin: 1,440 ± 116 mg./kg. body weight;

Dihydrostreptomycin: 1,600 ± 108 mg./kg. body weight (Rake *et al.*, 1948).

Local.—Experiments performed with animals, plants, protozoa (Florey *et al.*, 1949) and tissue cultures (Keilover, 1948) disclosed that only in very high concentrations did streptomycin have any deleterious effect.

Chronic.—Since, in the management of tuberculosis, prolonged treatment is so often essential, studies on the chronic toxicity of the therapeutic agents employed are of particular significance.

In man, the toxic effects accruing after prolonged dosage with either of the streptomycin compounds are confined to: (i) Eosinophilia, sometimes associated with changes in the skin. (ii) Damage to the VIII nerve.

Allergic reactions.—Cohen and Glinsky (1951) formed the opinion that although streptomycin was not a primary skin irritant, hypersensitivity commonly developed, especially in those handling it.

According to Burn and Westlake (1949) the sensitization reactions to dihydrostreptomycin alone are much less common than those associated with the parent compound. What is more, the antigenic nature of the two substances is distinct. Consequently, in a patient already sensitized to streptomycin, the dihydro-derivative may be substituted without fear of continuing allergic manifestations.

Neurotoxicity.—With both streptomycin and dihydrostreptomycin this is confined to VIII nerve apparatus lesions.

In general, the degree of damage is related to the adopted dosage and to the blood levels obtained. The consensus of opinion now is that, provided a pure preparation is chosen and provided there is no incidence of renal damage which might occasion unduly high serum concentrations of the drug, 1 gramme streptomycin may be given daily for up to sixty days without any serious risk of neurotoxic consequences (1949, *Brit. med. J.*, i, 1043).

What is particularly fascinating about this subject, at any rate academically, is the way in which streptomycin affects principally the vestibular apparatus, while the toxic impact of dihydrostreptomycin falls upon the auditory mechanism.

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Professor F. C. Ormerod:

The original administration of 3 grammes a day of streptomycin produced deafness in a number of patients and vertigo in the majority. Reduction of the dose to 2 grammes daily abolished the deafness but vertigo occurred in two-thirds of the patients. Further reduction to 1 gramme lowered the incidence of vertigo to one-sixth of patients.

It was found that the vertigo began after 20 or 30 grammes had been administered. Some patients showed nystagmus but no vertigo and others vertigo but no nystagmus. In most cases, however, the two signs occurred together. It was noticed that in most cases there was reduction, if not loss, of response to caloric stimulation. Where the caloric responses were normal it could be safely assumed that the vertigo would disappear. When the responses were absent it was unusual, but not unknown, for recovery to take place. If the responses were reduced there was reasonable expectation that they would improve. Where the caloric responses disappear during the course of treatment, in the majority of cases they do not return. When tested at the end of the course of treatment these patients give a normal response to galvanic testing which suggests that the damage is in the sensory end-organ and not the nerve tracts. When tested a year later it was found that a few patients had lost their response to galvanic stimulation which suggested that secondary degeneration had taken place. When tested again after three years there were no further degenerative changes, but a few had improved so that the caloric responses could be obtained, which suggests that the changes are reversible in some cases.

Streptomycin only causes deafness when large doses of the drug have been given over long periods, such as 3 grammes daily for 120 days (Glorig). In such cases a degree of perceptive deafness occurs.

The vertigo seemed to be such a serious drawback to the use of streptomycin that work was done on variants of the original substance. Dihydrostreptomycin was evolved and it was claimed that this substance did not harm the inner ear and that its therapeutic effects were as good as those of streptomycin. It is true that vertigo hardly ever results from administration of dihydrostreptomycin but it has been found that perceptive deafness very often occurs. It may appear late in the course of treatment or even after the course is completed. The loss of hearing is severe and seems to be irreversible. The claim that it has better therapeutic effects than streptomycin does not seem to be borne out. The changes in the vestibular apparatus caused by streptomycin are ameliorated or disappear owing to compensatory adaptation and in many cases are not frequent or marked. The severe perceptive deafness caused by dihydrostreptomycin is a much more serious disability and there seems to be no excuse for the continued administration of this drug.

The site of the lesion: At first it was thought that the toxic lesion caused by streptomycin was located in the nuclei of the two divisions of the VIII nerve in the hind-brain. This appeared to be confirmed by animal experiments in which degenerative changes were found in the hind-brain though the internal ears did not seem to have been examined in these cases. The amount of the drug used in these experiments was out of proportion to any possible therapeutic amount. In one series guinea-pigs were given amounts in three to four weeks that would have been equal to 600 grammes in man—about twenty times the normal dose. In some animals the general toxic effects were such that the animals died before any part of the VIII nerve system was involved. In some cases of this heavy dosage there were lesions in the central nuclei and in the end-organs and in others in the nuclei only.

Further experiments have been carried out by Luzius Rüedi, Raoul Caussé, Aram Glorig and particularly by Karl Berg in which relatively therapeutic doses have been given to a series of animals. It has been shown that the majority of the changes take place in the organ of Corti, in the ampullæ of the semicircular canals and the end organ of the saccule and utricle. In some animals there were changes in the bulbar nuclei but these were found only in animals which had been allowed to survive the administration of the drug for several months. These authors are all of the opinion as a result of these recent experiments that the primary effects of the drug involve the end-organs and destroy them. As a result of the destruction of the end organ degeneration in the neural portion of the system takes place and shows itself in changes in the bulbar nuclei.

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Miss Edith M. Whetnall and Dr. H. A. Lucas: *Changes in the Internal Ear and VIII Nerve in Fatal Cases of Tuberculous Meningitis treated by Streptomycin and Dihydrostreptomycin.*

We have been fortunate in obtaining through the kindness of Dr. W. L. Calnan a small series of temporal bones from cases who have died from tuberculous meningitis and who have had treatment with streptomycin or dihydrostreptomycin.

The temporal bones have been fixed and decalcified in the usual way and embedded in celloidin. Serial sections have been cut and consecutive ones including the internal ear and VIII nerve have been stained and examined. The following cases are typical:

(1) D. H., boy aged 6 years. This child was treated for miliary tuberculosis for four months with intramuscular streptomycin 1 gramme daily. Treatment was discontinued for a month and he then developed tuberculous meningitis for which he was treated for six months with intramuscular and intrathecal streptomycin, followed by a further four months of intramuscular streptomycin which resulted in clinical recovery. He unfortunately died from acute appendicitis and peritonitis. At this time there was no evidence of tuberculosis and he was not deaf. The cochlea, vestibule and VIII nerve were normal.

(2) C. G., boy aged 6 years. This boy suffered from tuberculous meningitis and was treated for twenty-eight days by intramuscular injections of 2 grammes daily and by intrathecal injections of 50 mg. of streptomycin daily. The cochlea showed considerable lymphocytic infiltration which included the basilar membrane, organ of Corti, Reissner's membrane and the lateral wall of the scala media. There is a massive infiltration of the sheath of the nerve and at the junction of the cochlear and vestibular portions.

(3) H. M., girl aged 3, suffering from tuberculous meningitis. Intramuscular injection of streptomycin 1 gramme daily for four months and 2 grammes daily for final one and a half months. Also 50 mg. intrathecally for final one and a half months. In this case the cochlea was practically normal, but there was infiltration of the ganglion of the vestibular nerve by tuberculous granulation tissue and in the tissue of the nerve towards its cephalic end. (Fig. 1.)

(4) J. W., girl aged 5, suffering from tuberculous meningitis. Treated by 50 mg. of dihydrostreptomycin daily intrathecally and 1 gramme intramuscularly for eight weeks. The cochlea and vestibule are normal but there is massive infiltration of the sheath of the VIII nerve with endothelioid cells, lymphocytes and giant cells. There is some lymphocytic infiltration of the nerve itself. (Fig. 2.)

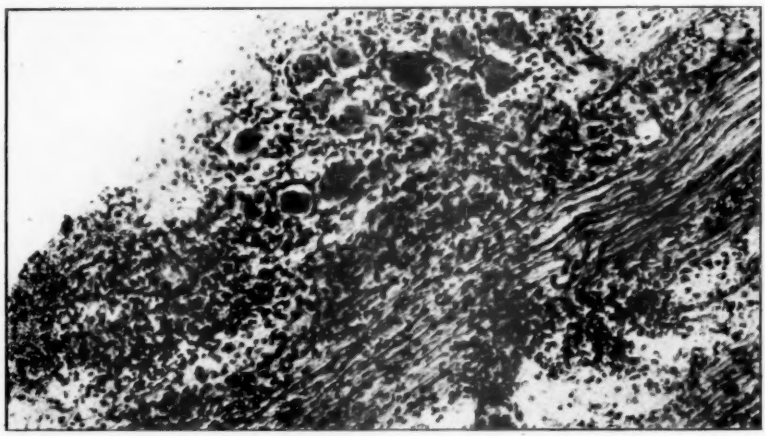

FIG. 1.—Tuberculous infiltration of vestibular nerve and vestibular ganglion. × 170.

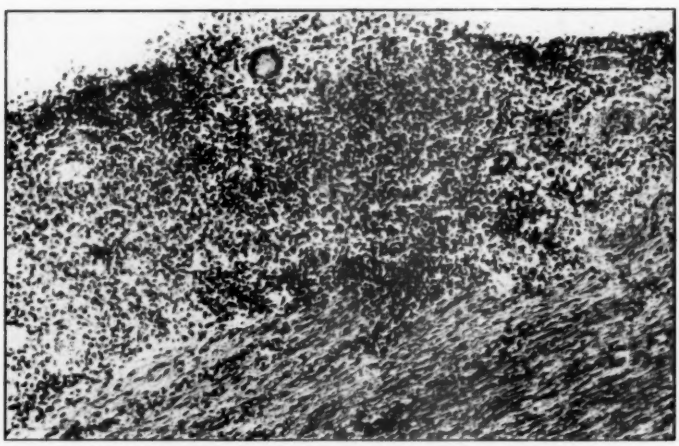

FIG. 2.—Tuberculous infiltration of cochlear nerve. × 135.

Summary.—The striking feature about these sections is the extensive tuberculous infiltration in the sheath of the VIII nerve. This is similar in all of them in spite of the varying lengths of time of treatment with the one exception who had recovered and died from appendicitis. Any slight changes in the cochlea are difficult to evaluate and it is not certain that they can be attributed to the toxic effect of the streptomycin. It may be that they are caused by a toxic irritation due to the tuberculous affection of the nerve in the immediate neighbourhood, or to some neurovascular change, again caused by the disease in the nerve. The lymph-cell infiltration of the structures of the cochlea confirms the suggestion of tuberculous toxæmia. It is realized that this is only a very small series but it was thought that the findings would be of interest. The suggestion has been made that deafness in some cases may be due to the meningitis and not to the antibiotic. The incidence of deafness in cerebrospinal and pneumococcal meningitis confirms this view and the rareness of deafness following streptomycin when given for other forms of tuberculosis supports it. The gross changes seen in the cochlear and vestibular nerves in these sections explain how deafness and vertigo can be produced.

Mr. A. S. Walker: *Hearing of Patients after Tuberculous Meningitis.*

Since September 1950 the Audiology Unit at Golden Square has had the opportunity of seeing some 93 patients who have recovered from tuberculous meningitis following streptomycin and dihydrostreptomycin treatment. Most of these patients (76) received streptomycin; a small number (6) had dihydrostreptomycin sulphate, and the remaining 11 cases started treatment with dihydrostreptomycin but later changed to streptomycin when the toxic effects of dihydrostreptomycin were made known.

A full history was obtained on each case from the various hospitals concerned. An examination was made of the Ear, Nose and Throat. Tests of hearing and investigation of the vestibular reaction were carried out.

The following classification was used for assessing the degree of hearing loss.

(1) Total Deafness. Hearing nil. No response to loud sounds close to the ear even when amplified. No response to audiometry.

(2) Subtotal deafness. Hearing for loud sounds only, e.g. drum or castanet.
A few "islets of hearing" may be found for pure tones, e.g. 128, 256, 512 at high intensity. Vowel discrimination may be absent or incomplete.

(3) Partial deafness—severe loss. A conversational voice cannot be heard at 3 ft.
Hearing is lost for consonants but is present for vowels. Audiograms show a severe loss, 70 decibels or more in the speech range.

(4) Partial Deafness—moderate loss. A conversational voice can be heard at a distance of 3 ft. and up to 10 ft. Audiograms show a marked loss, in many cases up to 40 decibels.

The test material consisted of word lists and sentences prepared by Fry and Reed.

Caloric vestibular tests were carried out in the method described by Fitzgerald and Hallpike (1942).

Galvanic tests were carried out using the method described by Bignall, Crofton and Thomas (1951).

Dosage.—Although the patients seen came from various hospitals the dosage was more or less uniform. The intrathecal dose was 50 mg. daily for all except a few of the earliest cases who had 100 mg. daily. The intramuscular dosage was 20 mg. per lb. body weight daily in two doses twelve-hourly in most cases, but some had 1 gramme daily in two doses twelve-hourly. PAS (sodium para-aminosalicylate) was given throughout in all cases. Dihydrostreptomycin was given in the same amounts as streptomycin.

At the outset the cases were unselected and consisted of all the cases treated at the Highgate Wing of the Archway Hospital Group. The incidence of deafness in this series of 30 cases was just under 37% and of these 17% were subtotally deaf. Following this practically all the patients were referred because of suspected deafness.

There was a most significant rise in the incidence of deafness amongst those 17 cases who had received dihydrostreptomycin, or dihydrostreptomycin and streptomycin—more than 65% of these cases being severely deafened.

Calorics: In 10 patients who had normal hearing or suffered from a slight degree of deafness, 9 had a minimal response and 1 a diminished response. All the others tested had no response to cold caloric irrigation. The galvanic and Romberg's tests were positive in all cases. Some 15 cases have been re-tested within the last few weeks to observe if there had been any changes over a period of eighteen months, but the galvanic and caloric responses were unaltered from the original testing.

The onset of deafness was frequently heralded by a roaring tinnitus, and when this had subsided some degree of deafness was noted. In the great majority of cases this was slight at first, gradually increasing for two to three weeks, and then suddenly becoming much more severe in the fourth week (often then subtotal). Other cases had an insidious onset, the deafness gradually increasing over a period of three to four months. One adult treated throughout with dihydrostreptomycin sulphate became subtotally deaf in a period of seven days during the seventh month of treatment. In 8 patients no deafness was suspected on discharge from hospital, but became apparent some months after returning home—in 1 the deafness being slowly progressive over a period of six months.

The critical time for the onset of deafness was the fifth to sixth month, but in a few cases it was observed as early as the third month or as late as the fifteenth month after starting treatment.

Because of the possible onset of deafness from the fifth month one of the Units started giving a course of 100 consecutive daily injections intrathecally with no rest periods (this together with the usual intramuscular streptomycin and PAS). At the end of this period a very thorough clinical examination was made, and whenever possible a rest period of two to three weeks given. A further clinical examination was then made and if the patient's general condition permitted, the streptomycin was either stopped or re-started on alternate days.

Some of the earlier cases, although suspected of being deaf, were not seen until the patients were in a stage of convalescence and ready to leave hospital. The result of this was that many who suffered from severe deafness had marked voice changes and in the younger age groups speech was lost.

The importance of patients being seen as soon as possible after the onset of deafness cannot be sufficiently stressed. Auditory training and lip-reading with the help of a hearing aid must be started at once.

As a result, many of the children in this series have returned to an ordinary school instead of a school for the deaf.

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Mr. Terence Cawthorne: *Streptomycin and its Use in Ménière's Disease*

When it was found that streptomycin had a toxic effect upon the VIII nerve system, and in particular upon its vestibular division, the possibility of using this toxic effect therapeutically in cases of Ménière's disease was naturally considered. It had been shown that both sides of the vestibular system were equally sensitive to streptomycin, so this meant that if it were to be used in the treatment of Ménière's disease vestibular function on both sides would have to be sacrificed.

Hamberger and his colleagues found that the effects of bilateral vestibular failure following streptomycin therapy were easily overcome in children, fairly easily in young adults and seldom from middle age onwards. E. P. Fowler, Jr., pointed out that the effect of treating Ménière's disease with streptomycin was the same as a bilateral section of the vestibular nerve; and warned against its use in patients over 50 for the same reason as given by Hamberger. He also advised against using it for unilateral disease. Rüedi believes that the toxic effect is of the end-organ itself and not, as is held by many, upon the ganglion cells and nuclei. He considers that it may prove to be a valuable method of treating Ménière's disease and advises its use in small doses so that vestibular function is depressed without being entirely lost. My own feeling about this is that symptoms from a disordered labyrinth will continue so long as any vestibular function remains. Winston and others have pointed out that the toxic effect may not be confined to VIII nerve centres in the central nervous system alone.

It has generally been found that 2 to 3 grammes daily for twenty days are sufficient to abolish vestibular function, but my experience has been that even with 3 grammes of streptomycin a day for thirty days vestibular function has not always been entirely abolished. In the last 4 patients to whom I gave streptomycin, vestibular function could not be abolished despite prolonged medication.

Little is, as yet, known about individual sensitivity to streptomycin. There is, however, some reason for believing that the vestibulo-toxic properties of streptomycin vary from brand to brand and possibly even from batch to batch. In my experience some of the earlier batches of streptomycin were much more toxic to the vestibular system than later ones, whilst it has, of course, been found that the dihydro compound which was chosen for its comparative lack of vestibulo-toxic properties has given much more trouble because of its effect on hearing.

Thus the problem is not quite so straightforward as it may at first sight appear, and streptomycin should not be used without considering the disadvantages that may accompany its use, and the fact that it may not work. A prolonged course of injections with streptomycin is not always well tolerated by patients, and one cannot even encourage them to persevere with the certainty that vestibular function will be entirely abolished. Even when this is achieved, the difficulty of compensating for bilateral loss of vestibular function may be great, particularly from middle age onwards. It must also be borne in mind that Ménière's disease affects the cochlear as well as the vestibular apparatus and, in bilateral cases, the cochlear symptoms may cause the greater distress and discomfort.

Streptomycin should not be used in the treatment of unilateral Ménière's disease. In bilateral cases it should only be considered in younger patients when all other measures have failed to control the attacks.

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Section of Otology with Section of Laryngology

JOINT SUMMER MEETING WITH THE NORTH OF ENGLAND OTOLARYNGOLOGICAL SOCIETY HELD AT MANCHESTER ROYAL INFIRMARY

OTOLOGICAL SESSION

[*June* 13, 1952]

Chairman—G. E. ARCHER, M.B., Ch.B., F.R.C.S.Ed., D.L.O.
(President of the Section of Otology)

Hearing by Bone Conduction and the Use of Bone-conduction Hearing Aids

By T. S. LITTLER, M.Sc., Ph.D., J. J. KNIGHT, B.Sc., and P. H. STRANGE, B.Sc.

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SUMMARY

THE exact nature of the communication of sound to the inner ear by bone conduction is somewhat obscure although the experimental work of Békésy (1932), Bárány (1938) and others offers suggestions of possible explanations of this means of stimulation. The relationship of the "occlusion" effect as observed when the meatus is plugged externally and internally and the effect of restriction of the conductive mechanism is discussed. It is suggested that in normal subjects and patients with perceptive deafness hearing by bone-conductor stimulation occurs virtually by means of the normal air-conduction mechanism due to the inertia of the free ossicular chain. In conductive deafness stimulation may be by direct excitation of the bony structure of the cochlea with the inertia of the cochlear fluid operative if the round window is unobstructed. In advanced stages of otosclerosis the obstruction of both windows would be expected to indicate an apparent perceptive element, i.e. a lowered bone-conduction audiogram. An account is given of experiments relating to the communication of sound from one ear to the other. When sound from a telephone receiver is applied to one ear the level of sound communicated to the other ear known as "cross-hearing" depends on the mode of application and the type of receiver. For a bone-conduction receiver applied to the mastoid there is in general very little difference in the level of sound reaching the two ears over the frequency range 250 to 2000 c/s. In the case of sound applied by an air-conduction receiver the communication of sound by "cross-hearing" suffers a reduction of 45 to 50 db. for an external receiver and 75 to 80 db. for an insert receiver. The importance of masking when making bone-conduction tests is emphasized and it is suggested that the application of the masking noise is accomplished most efficiently by means of an insert form of receiver.

The usefulness of bone-conduction hearing aids and the conditions under which their application is superior or preferable to air-conduction types is discussed.

INTRODUCTION

It would not be possible in this short paper to give great details of all contributions to the study of hearing by bone conduction but no treatment would be satisfactory that did not mention the fundamental investigations carried out by Békésy (1932) and Bárány (1938). The mode of conduction of sound by bone conduction is very complex and despite many researches its exact nature is not yet known. In the case of normals and some instances of perceptive deafness the stimulation virtually makes use to some extent of the normal air-conduction mechanism. The possible ways in which sound applied to the skull can stimulate the end-organ of hearing have been considered in great detail in the papers of Békésy and Bárány: Tumarkin (1946) has also dealt with this subject. It is generally accepted that in the normal mechanism of hearing via a movement of the stapes in the oval window the round window acts as a release valve, a physical necessity owing to the almost incompressible nature of the perilymph. It is also generally accepted, as a result of much direct and indirect evidence in favour of the place theory of hearing, that at specified frequencies definite regions of the basilar membrane receive maximal excitation corresponding to the motion, velocity or pressure of the vibration. It is probable that any specified element of the cochlea is controlled by the associated mass or length of the fluid in combination with the elastic constants of the maximally excited region of the basilar membrane and organ of Corti. A resonant element of this type usually means that the total path takes approximately the time of one vibration to be traversed by the sound and it is rather important to bear in mind this nature of resonant physical elements in the cochlea when one considers the excitation of the whole skull by means of a bone-conduction receiver.

Now let us consider the state of motion of the head when under the influence of a source of alter-

nating applied force such as the prong of a tuning fork or a bone-conduction receiver. The resultant motion is one due to the reaction between the forcing element and the head and it is influenced by the velocity of sound in the matter making up the structure of the head. If the head were homogeneous the problem would be a simple one and the form of motion could be easily determined. The principle is briefly this: if the wavelength of sound in the medium is larger than any dimension of the head then the particles of the head all move together in phase. They do not all move the same extent, however, and consequently there is some elastic distortion of the head. As the frequency is raised a state is reached at which the wavelength becomes smaller than the dimensions of the head and then we get points at which particles are vibrating in different phases and also regions over which the vibrations become minimal. Since the head is not made up of homogeneous matter there will be pockets where the velocity of sound is not the same as that in the skull, but so long as the dimensions of these pockets are small compared with the velocity of sound in their material they will vibrate with the skull as a whole. If, however, there are pockets of resonant elements such as parts of the cochlea or even the ossicular chain or resonant cavities such as might occur in the tympanic cavities or mastoid cells, then these elements will not vibrate with the head as a whole. It is indeed possible that in such a complex structure as the head individual elements vibrate with a motion greater or less than that of the driving force and even with a phase which is reversed with reference to this driving force. It is necessary to make these reservations to guard against any false conclusions which might arise by basing our arguments on observations obtained by measurements of the vibration of the skull as a whole. The results of measurements and explorations of skull vibration when under the application of a bone conductor are given in the papers by Békésy and Bárány. The vibrations according to Békésy are as follows: at 200 c/s and below, the skull behaves as a rigid body, near 800 c/s there is a null line in the middle with the two extremities vibrating oppositely in phase and at about 1500 c/s and above the skull vibrates in sections separated by nodal lines. This movement of the entire or part of the head will move its constituents with it unless as mentioned previously there are resonant or unrestrained elements involved. Under certain conditions resonant elements might tend to move less than the containing structure.

Mode of Excitation of End-organ

It has been demonstrated that identical vibration patterns of the cochlear partition occur for both air and bone conduction excited sound since a tone heard by one means can be cancelled by a tone heard by the other means by appropriate adjustment of intensity and phase. Also quite recently Wever and Lawrence (1952) have shown that a force applied at any region of the cochlea excites the associated region corresponding to the place principle.

Excitation of skull vibration by a bone conductor in the manner that has just been discussed does not suggest an efficient way of excitation of the end-organ. For, whereas the natural form of excitation using the stapedial motion causes relative motion between the cochlear fluid and the basilar membrane, in the motion of the skull as a whole as in bone conduction there is a tendency for the structure of the cochlea to move as a whole, except for the individual inertia effects of different elements previously referred to. The less rigidly these elements are connected to the skull the more these inertia effects will make themselves apparent. Thus if the stapes could be held fixed in space while the skull was vibrated this would tend to increase the inertia of the cochlear fluid and so increase the excitation of the end-organ. In other words, the most efficient way of excitation of hearing by bone conduction is to move the skull and hold the fluid stationary which is virtually the same mechanism as in hearing by air conduction where the skull is stationary and the fluid is moved.

Vibrations applied to the mastoid can also excite hearing by means of the normal air-conduction mechanism in so far as they will set the meatal wall into vibration thus communicating the vibration to the tympanic membrane.

Another way in which the end-organ may be excited is by structure-borne vibrations dilating and contracting the superficial structure of the labyrinth. In this way the cochlear fluid tends to be moved relative to the basilar membrane. Evidence for the likelihood of this lies in the production of nausea and dizziness when loud bone-conducted sounds excite the mastoid. In normal hearing or perceptive deafness without a conductive obstruction a certain degree of restraint is imposed because the ear drum and meatus are acted upon by the surrounding atmosphere. In conductive deafness, however, the ossicular chain would tend to be more rigidly connected to the bony structure of the skull and hearing by bone conduction may be influenced by the asymmetry due to the restriction of the oval window and freedom of the round window.

With these considerations we are forced to the conclusion that hearing by bone conduction is likely to be difficult except as a second order effect, and it is only to be expected that it will be favourably comparable with air conduction when the normal air-conduction path is defective or when some lack of symmetry in the mechanical features of the ear amplifies the second order effect which is responsible for bone conduction hearing.

According to Guild (1936) an important factor in bone conduction is the osseous pathway consisting of the bony trabeculæ of the subaditus region. Guild reported instances of subjects with normal air conduction but impaired bone conduction and demonstrated in post-mortem sections that fractures of all these trabeculæ had occurred in the subaditus region.

Experimental Observations

It is well known that when sound is applied to one ear by an air-conduction receiver there is a transmission of sound to the other ear across the skull with an average reduction of 45 to 50 db. in intensity. This is the so-called "cross-over" or "cross-hearing" effect. It is exemplified in the "shadow" audiogram of the pure-tone test of a patient with total or almost total hearing loss on one side or in patients with an advanced state of acoustic neuroma. Fig. 1 gives some examples of this type of result obtained on patients with hearing on one side only.[1] It is usual to assume that this is due to sound conducted by bone to the other ear but, as will be seen later, this definition of "cross-over" bone-conducted sound must be qualified. It is not so well known that when these tests are made with the air-conduction receiver connected to the ear by an insert tip or by the use of an insert receiver as the stimulating device, the "cross-over" effect is reduced to a level of about 80 db. below that of the applied sound as illustrated in Figs. 2 and 3, apparently indicating that the skull-communicated

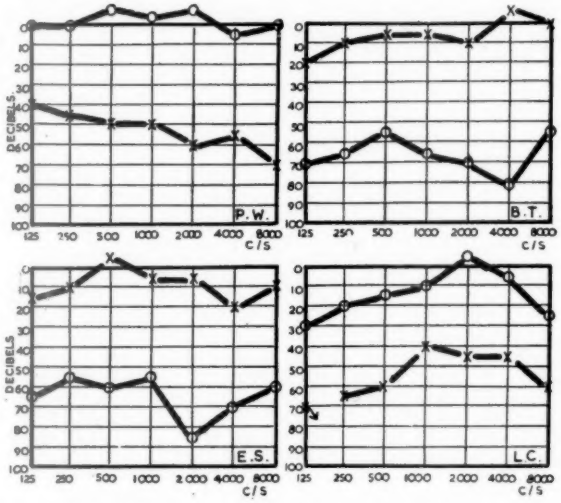


Fig. 1.—P.T. audiograms of patients having total deafness on one side (external A.C. receiver). Left ×—×. Right O—O.

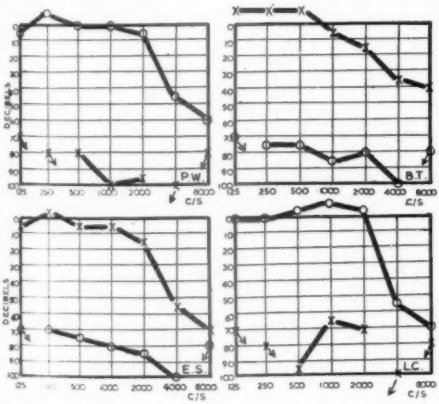


Fig. 2.—P.T. audiograms of patients having total deafness on one side (insert tip attached to acoustically screened A.C. receiver). Left ×—×. Right O—O.

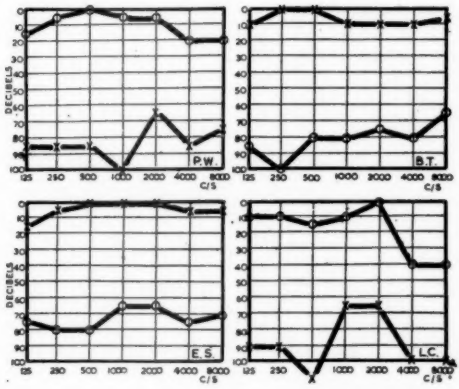


Fig. 3.—P.T. audiograms of patients having total deafness on one side (using hearing aid insert receiver). Left ×—×. Right O—O.

[1]We are indebted to Mr. L. R. S. Taylor, F.R.C.S., for placing many of these patients at our convenience for investigation.

sound gets in mainly via a portion of the auricle and the cartilaginous structure of the outer portion of the meatus. During the course of experimental work for the Electro-Acoustics Committee of the Medical Research Council (1947), Dadson measured the vibration of the skull for external and insert type receivers, and found that, for a given loudness level, it was considerably greater for the former type.

The Occlusion Effect

The "occlusion" effect whereby there is an apparent improvement of bone-conduction hearing of normal and perceptively deaf subjects when the external ear is blocked is made use of in the Bing Test for what is familiarly known as absolute and relative bone conduction. This effect is most striking at frequencies below 1000 c/s but it shows a tremendous variation from subject to subject and also from experimenter to experimenter and it is worth while to examine the effect together with other factors which may influence its magnitude. The vibrating bone-conduction receiver is a source of air-borne sound of which the intensity may be sufficient to be appreciably audible to the subject. In addition, the skull itself in vibrating is a source of sound of appreciable intensity which may produce a sufficiently intense sound to contribute appreciably to the subjective effect. Consequently when the meatus is occluded these contributions are eliminated. Since the "occlusion" effect is an increase of sensation these factors can only be appreciable if they are out of phase with sound conducted by direct bone conduction. Recent work by Ayers and Morton (1951) attempted to assess the magnitude of the effects and when exploring by a probe microphone they concluded that the main source of sound was within the ear canal itself. However, since the head in vibrating would carry the air particles in the meatus with it to some extent it would be expected that a fixed probe microphone would indicate a sound field in the meatus. It seems likely therefore that the clue to the "occlusion" effect lies in some modification of the movement of the air particles in the meatus. Békésy made tests with a plug, first, at the external opening of the meatus and, secondly, close to the eardrum. He claimed that very little "occlusion" effect occurred when the plug was near the eardrum. Békésy is of the opinion that the head of the mandibular joint is responsible for the "occlusion" effect when the opening of the meatus is plugged since it is not rigidly connected to the skull and its inertia would be more effective in compressing the air in the meatus when the latter is closed at the external end. Undoubtedly the mandibular joint has some influence as can be seen by the subjective changes in hearing by bone conduction when the jaws are clenched and released. Fig. 4 illustrates Békésy's contention and Fig. 5 the theory of the "cross-over" effect. Despite the various refinements in the explanation of the action of the "occlusion" effect the experimental evidence indicates that for the occurrence of the effect it is essential to have an unobstructed meatus. As to whether there is a requirement of a freely moving ossicular chain we must look to further experiment. Perhaps the most convincing evidence would be expected to come from results obtained with patients having slight hearing loss diagnosed on other grounds as conductive.

Now air-conduction and bone-conduction audiograms taken together on otosclerotic patients show that it is possible to have an air-conduction loss of as much as 40–50 decibels without any appreciable loss by bone as referred to normal. Further, that such patients do not show the "occlusion" effect. There are a very small number of deaf patients estimated at about 0·5% of those attending clinics for alleviation by hearing aids who hear speech better by bone conduction than by air. All these patients have audiograms which show a displacement of 40–50 decibels or more between air and bone conduction.

The suggestion that, more than any other, seems to fit in with these facts is that, in normal hearing and in deafness having no conductive loss, sound applied to the bone excites the inner ear mainly by the normal air-conducting mechanism, either by vibration of the tympanic membrane by the meatal wall vibrations or by what is really a case of relative motion; that is, due to the inertia of the air in the meatus and tympanic cavity and the inertia of the drum and ossicular chain, there is less motion of the oval window than of the supporting structure of the membranous labyrinth. Thus stimulation by bone is a rather inefficient way of stimulating by the normal air-conductive mechanism. It is therefore to be expected that direct air stimulation is the more effective mechanism. As the freedom of movement of the ossicular chain becomes restricted, as by ankylosis in otosclerosis, so all parts of the structure of the ear move together as a whole and the sensation is received due to relative motion between the solid structure of the cochlea and the cochlear fluid as governed by the inertia of the latter or by the various distortional or compressional means suggested by Békésy. The inertia of the fluid will be operative so long as the relief mechanism of the round window is patent. Should the round window's freedom be lost, as is possible in advanced otosclerosis, then communication by bone conduction will become impaired; thus we shall have audiograms showing both air-conduction and bone-conduction loss—in other words an apparent mixed deafness with the perceptive element possibly apparent. Now when we have reached the stage with a difference of 40 decibels or more between the air and bone conduction loss it seems very probable that sound applied by air conduction can only operate by truly bone-conduction mechanism, and it is at this stage that direct stimulation by a bone-conduction receiver may become more efficient, especially so if we take the insert receiver as the standard for air conduction. For in this state, air-conduction receiver stimulation depends on the surface area

of stimulation. When the conductive mechanism has become so seriously impaired that we have what may be called the apparent perceptive element, the normal mechanism of stimulation is no longer possible as the whole cochlear fluid is encased in bone. It is conceivable that the tuned elements of the end-organ can then be stimulated by shock excitation somewhat similar to that of a suspended

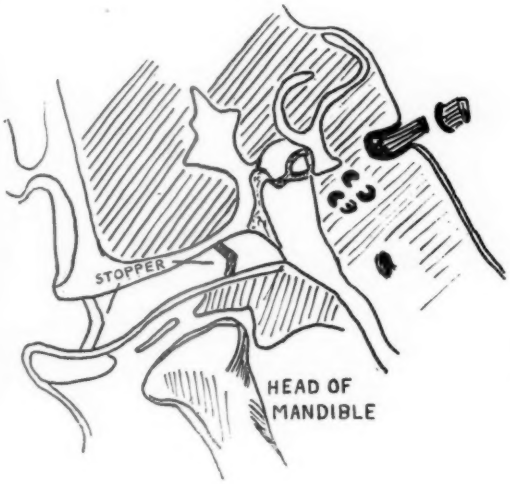
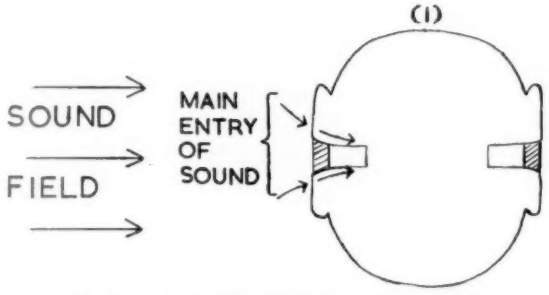
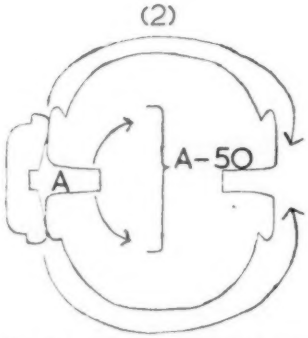


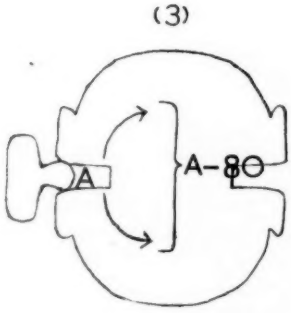
FIG. 4.—Section of head showing position of mandibular joint. Stopper near open end of meatus gives much larger "occlusion" effect than stopper near eardrum (*after* Békésy).



Maximum insulation of best stopper (30–45 db.).



Total "cross over" of external receiver (approx. 50 db.—250–1000 c/s.)



Total "cross over" of insert receiver (approx. 80 db.—250–1000 c/s.)

FIG. 5.—"Cross-hearing" effect. Advantage of insert receiver.

element in a closed flask which is shaken vigorously. Of course the mechanism is a very inefficient one and this probably accounts for the reason that speech with this type of lesion requires enormous powers.

Application to Audiometry

Arising out of the experimental results which have just been discussed we put forward the following suggestions regarding their application in audiometry.

(1) That, when making bone-conduction tests, masking should be applied to the ear not under test, since bone-conducted sound is conducted almost to the same extent to both ears. This is now common practice.

(2) That masking should be applied to the better ear for air-conduction tests if there is a difference of 40 decibels or more in the unmasked air-conduction tests on account of the "cross-hearing" effect.

(3) That masking is accomplished more efficiently by means of a nipple-conducted source or insert receiver than by an external receiver.

(4) That nipple-conducted sound is potentially better for air-conduction tests on account of the smaller amount of sound transmitted by bone to the untested ear.

(5) The great importance of considering the bone-conduction audiograms together with the air-conduction audiograms and the requirement of normal standards for bone-conduction hearing. The most desirable condition for bone-conduction testing seems to be to test in quiet conditions with the ear unoccluded. For only by this means can one ensure the differentiation between slight perceptive and conductive deafness.

(6) Observations should be made of the occlusion effect.

These suggestions are summarized in Fig. 6.

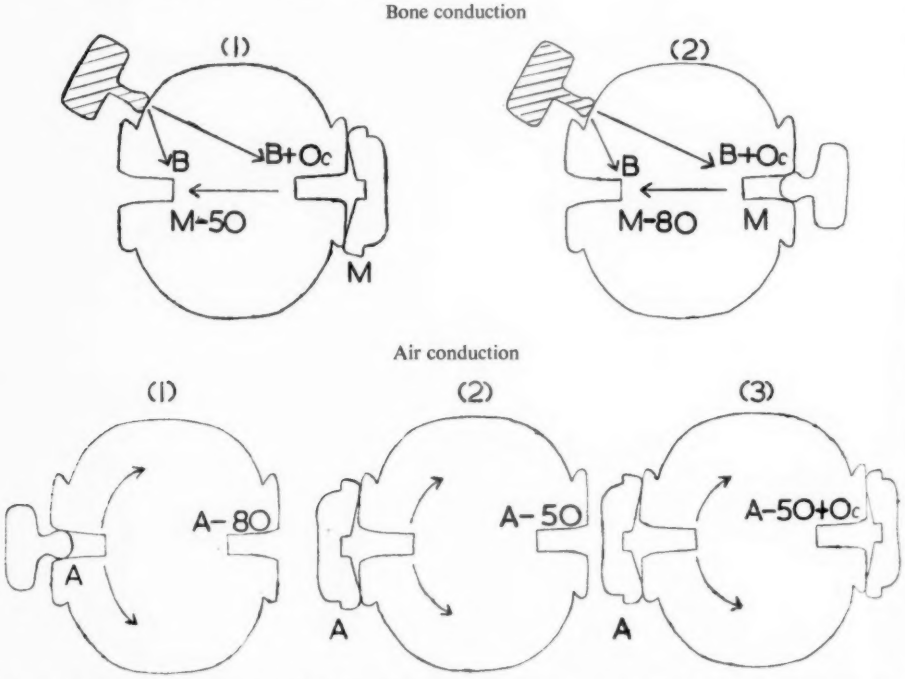


FIG. 6.—Masking in audiometry. When masked ear is covered "occlusion" effect tends to exaggerate "cross-hearing" effect.

It should be pointed out that the design of a bone-conduction receiver free from air-borne radiation is very important for audiometry. The most satisfactory designs so far have been those of the prod type having a button pressing on the mastoid and a rather heavy structure. This will always have advantages as compared with the type used in bone-conduction hearing aids for it is mainly the relative masses of the head and the driving structure that governs the relative amounts of vibration of the two. There is, however, no reason why a hearing-aid type of receiver should not be used provided

it has a high ratio of bone-communicated to air-radiated sound. In this type of receiver it is very important to avoid contact with the pinna or an abnormal amount of sound may be transmitted by air conduction.

The Use of Bone-conduction Hearing Aids

A very small section of the deaf community—we estimate the number as between 0·5% and 1% of deaf patients attending deafness clinics for alleviation by means of a hearing aid—are found to hear satisfactorily by means of a good bone-conduction aid only. They are undoubtedly of the type previously discussed and examples of their audiograms are given in Fig. 7. It can be seen that

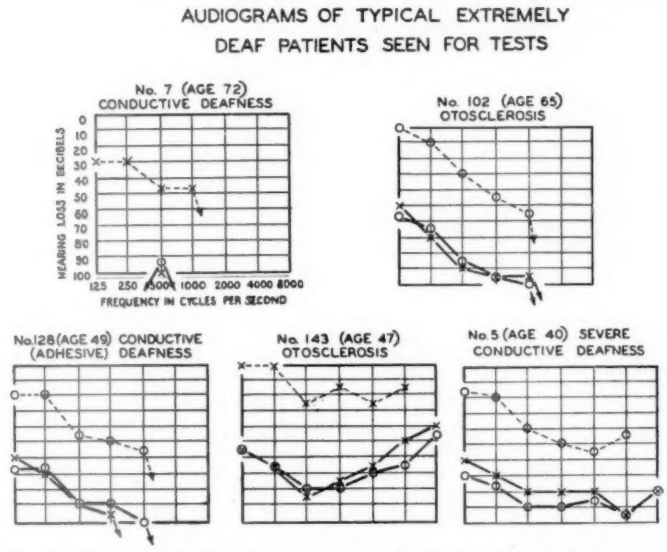


Fig. 7.—P.T. audiograms of patients for whom bone-conduction type of aid gives better articulation.

they are seriously deaf and that their bone-conduction audiograms are 40 to 60 db. above their air-conduction audiograms. Despite their appraisal of the bone-conduction aid they hear a very inferior and distorted version of speech and often the additional help of lip reading is very desirable. A second group of patients for whom bone-conduction aids may be indicated are some of those who are recommended to use an external receiver on medical grounds such as chronic discharging ears. These patients again have a smaller hearing loss by bone than by air and when the difference is 40 db. or more the good bone-conduction aid may prove to be the more useful form. External receiver aids have one main drawback; owing to the difficulty of acoustic feedback which is caused by an insufficient seal on the ear and due to sound radiated from the case of the instrument there is a limit to the amount of effective amplification that is obtainable. Feedback from the bone conductor is not so serious and in the special cases we have mentioned great effective amplification is sometimes obtainable from the bone-conductor aid. It cannot be too strongly emphasized that bone-conductor aids are only satisfactory when they use a really efficient bone-conduction receiver of which there are only two or three types at present available. So narrow is the reserve of sensitivity available that a reduction of efficiency of 10 decibels on the present best receivers makes all the difference between a useful and a relatively unusable instrument. In some instances the excitation of both ears by a single bone-conduction receiver is definitely advantageous.

It will be noticed that most of the patients for whom the bone-conduction aid is the most desirable have a far greater loss for high frequencies than for low. Such patients can only expect to make use of the frequency range over which the auditory system is an efficient receptor. Fortunately it is possible to obtain a satisfactory degree of intelligibility with the range of frequencies from 400 c/s to 1500 c/s. It is probably this range that the bone-conductor patients make use of most and in addition they may make use of other characteristics of speech such as the time build-up and decay of sounds to give them other clues which, together with lip reading, enable them to make the most of the information received.

There is evidence that when patients once begin to use a bone-conduction hearing aid they never like to return to the use of an air-conduction type and quite frequently they do not seem to like any adjustment of the frequency response of their own aid, as though they have become accustomed to

the interpretation of that particular form of response and stimulation. In the tests which are being carried out to get an idea of the most desirable response for hearing aids this apparent ability of the auditory system to adapt itself to a particular response sets us various problems. One cannot be sure that articulation from what might otherwise be the optimum response is not influenced by the listener being unaccustomed to it. Perhaps the most crucial tests will be those with patients who have not heard for a long time. At the present time the most pressing requirement is that of power efficiency. Should this become solved the question of frequency response can then be further investigated.

ACKNOWLEDGMENT

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Masking in Pure-tone Audiometry

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IT is a common experience that when any sound is applied to an ear it decreases the ability of that ear to perceive other sounds. If, while one sound is being applied to an ear, a second sound is gradually increased in intensity until the first sound can no longer be heard, the first sound is said to be masked by the second sound (Fletcher, 1929).

This commonplace observation can be put to good use in clinical audiometry where it is often imperative while testing one ear to prevent perception of the audiometer tones by the other ear. In air-conduction audiometry, for example, if there is a large difference between the thresholds of the two ears, the sound applied to the deafer ear may be perceived by the opposite better ear, and the familiar shadow audiogram will result. Only by masking the hearing of the intruding better ear can this effect be prevented. Similarly in bone-conduction testing, even in a case where one labyrinth has been deliberately destroyed by surgical means, the sound stimulus will be perceived whichever mastoid the bone conductor is placed on, because even when the bone conductor is applied to the deafened side the sound will be transmitted to the good ear, almost without loss. In bone-conduction audiometry the untested ear should always be masked. Two other types of hearing test where, in many cases, accurate results can be obtained only when the untested ear is masked are speech audiometry and recruitment detection.

The importance of masking as a necessary adjunct to monaural hearing testing has long since been recognized and a variety of ingenious methods have been tried. One of the earlier and best-known examples is the noise box of Bárány, a device still in everyday use. Other suggestions include the use of streams of air or water directed into the ear to be masked. Others have proposed for use as a masking sound a pure audiometer tone of the same frequency as the audiometer test tone; and at least one commercial audiometer has incorporated this method of masking. Many modern types of audiometer use mains hum for masking, while quite recently Zwislocki (1951) has utilized as a masking sound the audiometer tone itself, modified in a fashion to be described later, which is intended to make it distinguishable from the audiometer test tone.

Before discussing the relative merits of these methods and of our own suggestions, let us examine the features theoretically desirable in an ideal masking sound. Two different masking sounds which we may designate A and B may be equally effective in masking a given audiometer tone, but none the less the masking sounds A and B may differ markedly in loudness. It is obviously undesirable to have an unnecessarily loud masking sound, and we may therefore at this stage introduce a new term, the Masking Efficiency of a sound. This we define as the relation between a sound's ability to mask and

[1]Holder of a grant for research awarded by the Medical Research Council.

its loudness. A sound with high masking efficiency is one with good masking ability but minimal loudness. This then is the *first* desirable feature of an ideal masking sound, it must be efficient. A second requirement is that the masking sound must, for two reasons, be readily distinguishable from the audiometer test tone. First, it is a great advantage to be able to describe the two sounds to the test subject in terms which will not confuse him, and secondly, the test subject must from the description given him be able to recognize and distinguish the two sounds when he hears them simultaneously. This argument is all the more important when testing deaf subjects suffering from diplacusis.

The third, but by no means least important, desirable feature is that any apparatus required shall be as inexpensive as possible, and simple to operate.

Recapitulating, the three desirable features in the light of which we shall examine the usefulness of the various masking sounds are: (1) Masking efficiency; (2) distinguishability of masking sound from audiometer tone; (3) simplicity in use and manufacture.

It is scarcely necessary to enumerate the many objections to the use in audiometry of such masking devices as the Bárány noise box and jets of air or water. They are unpredictable in effect and awkward in use.

The objection to the use of a pure-tone masking sound having the same frequency as the audiometer tone is that there will be grave difficulty in distinguishing the two sounds. This difficulty can be decreased by introducing a difference between the frequencies of the masking and the masked tones. But as the difference between the two frequencies is increased so the efficiency of the masking sound decreases, and if the frequency difference is made large enough to permit ready distinction, the efficiency will be very low, or in other words the masking tone will have to be very loud to produce a given masking effect.

The masking of one audiometer tone by means of another tone of markedly different frequency is the principle underlying the use of mains hum as a masking sound. Here the masking sound, provided by the mains electricity supply, is a pure or near-pure 50 c/s tone. The apparatus required for the generation of mains hum is extremely simple, and there is no difficulty in distinguishing the masking sound from the audiometer test tone; but the hum will frequently need to be unpleasantly loud in order to produce a relatively small masking effect. This principle is used, however, with some slight modifications, by several audiometer manufacturers, one of whom claims that the masking effect of this type of noise is uniform for all the audiometer test-tone frequencies, and implies that the effect is independent of the type of deafness present in the ear to be masked. But our investigations of this type of noise have demonstrated its extreme unreliability. With a given amount of masking noise the masking effect produced upon a group of deaf subjects at each of the audiometer test-tone frequencies was found to vary almost at random by as much as 40 db., even after allowing for their different degrees of deafness (Fig. 1).

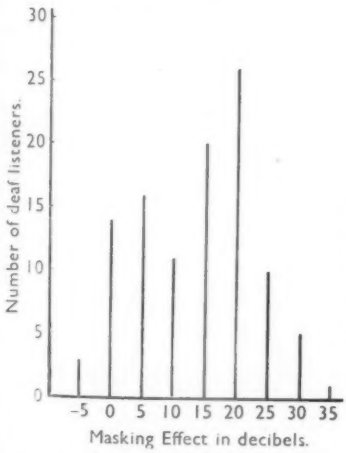

FIG. 1.—The masking effect (decibels rise in audiometer test-tone threshold) produced by modified mains hum upon a series of deaf listeners, at various test-tone frequencies and at a sensation level of 30 decibels (i.e. 30 decibels above the deaf subject's threshold for the mains hum).

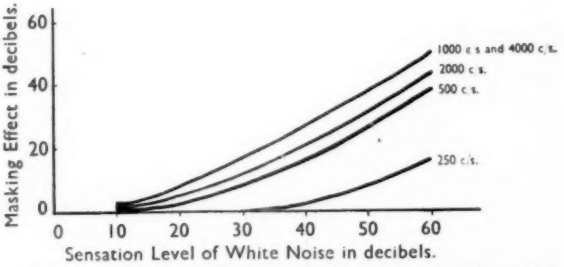

FIG. 2.—The masking effect (decibels rise in test-tone threshold) produced by white noise upon a series of normal listeners, at various test-tone frequencies and at various sensation levels (decibels above the tested subject's threshold for white noise).

The presence in this noise of numerous harmonic components makes it impossible accurately to predict its masking effect upon a deaf subject whose pure tone threshold audiogram is not flat.

Another type of masking noise we mentioned is that proposed by Zwislocki. In this method part of the audiometer output is led to the tested subject in the usual fashion, but the remainder of the output is modified with the help of mains hum in such a way that what was a single pure tone becomes a collection of different tones of slightly differing frequencies. This relatively simple manœuvre produces a masking sound which is efficient (in other words to produce a given masking effect it does not have to be excessively loud) but our experience has shown that many tested subjects, deaf and normally hearing alike, experience considerable difficulty in distinguishing the masking sound from the unmodified audiometer tone. We have already emphasized that for ease of testing it is desirable that the masking sound be readily distinguishable from the audiometer tone.

At this point it has become apparent that there may be room for improvement upon the masking methods we have reviewed. The major weak points in the masking sounds we have considered have been either poor masking efficiency, or difficulty of distinction, or a combination of both these faults.

The simplest way of providing ready distinguishability is to ensure that the masking sound shall always appear to be a definite *noise* when compared with the audiometer *tone*. Now a readily available type of noise having no resemblance whatsoever to a pure tone is white noise or random noise. It consists of a mixture of tones in which all audible frequencies are present in equal amounts, and its production involves only the most elementary electrical apparatus. Used without any modification white noise does exert a masking effect and it is readily distinguishable from all the audiometer tones (Fig. 2).

But the masking effect of white noise depends to an unpredictable extent upon the shape of the tested subject's audiogram, and it is at best very inefficient. These two objections to the use of white noise as a masking sound can be overcome by filtering it in such a way that only those frequencies which are near to the frequency of the audiometer test tone remain. Thus, instead of containing all audible frequencies it will contain a band of relatively few frequencies centred around the test-tone frequency (Fig. 3), and by using a variety of different filters the frequency at which the band centres can be varied. Such a filtering process will result in a masking sound much more efficient than unmodified white noise and much less dependent in its effect upon the shape of the audiogram. But if this process of filtering is carried too far and the band of frequencies left after filtering is too narrow, the resulting filtered noise will assume a tonal quality.

A number of tests were made to find out how far this filtering process can be carried; that is to say, how wide must the noise band remain in order to ensure that the noise does not lose its essential noise-like character and become a tone. We found that the white noise could be restricted to a band one-third of an octave wide and could still, in practice, be recognized as a noise by the vast majority of listeners. Any narrower band produced a sound with a readily recognizable tonal rather than noise quality. These observations led us to investigate further the suitability of one-third of an octave wide noise bands for use as masking sounds. Five of them centred about 250, 500, 1000, 2000 and 4000 c/s respectively were tested upon a group of normal and deaf subjects. It was found that the masking effect of all five noises upon their respective test tones was consistent and could be predicted in practice with accuracy, irrespective of the shape of the tested subject's audiogram (Fig. 4).

Further, determinations of the loudnesses of these noise bands, and of the other types of masking sound that we have mentioned, by means of the familiar loudness balance technique showed that, for a given masking effect, the one-third of an octave wide noise bands are as efficient as the best of the other masking sounds (Fig. 5).

TABLE I.—SHOWING LOUDNESSES IN SONES OF VARIOUS MASKING SOUNDS WHEN A 20 DECIBEL MASKING EFFECT IS PRODUCED

(Relative Masking Efficiency $= \frac{1}{\text{Loudness in sones}}$)

	Frequency of audiometer test tone to be masked				
Type of masking sound	250 c/s	500 c/s	1000 c/s	2000 c/s	4000 c/s
Modified mains hum	(beats)	10	8	19	57
Zwislocki noises	27	4	3	0·6	0·6
White noise	200	40	15	27	15
Third of an octave noise bands . .	2	1·0	0·7	1·0	1·0

The first of the three desirable features which an ideal masking sound should display is efficiency, i.e. the sound should provide good masking effect but be as quiet as possible. On this score, as we have just pointed out, the one-third of an octave noise bands are the most suitable of the various sounds we have reviewed. So far as the second criterion is concerned, these third of an octave bands are, as our experiments have indicated, noises rather than tones, and will therefore be readily distinguishable from the audiometer tones which they are intended to mask. There remains for consideration the third criterion, namely that the masking method shall be simple in use and require a minimum

Sensation Level of 1000 c/s tone

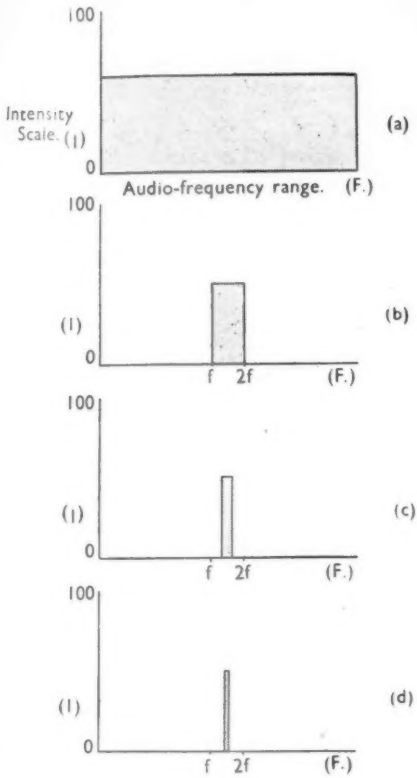

FIG. 3.

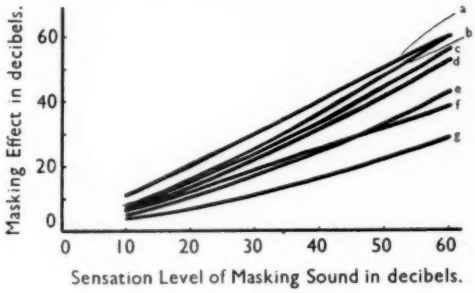

FIG. 4.

FIG. 3.—Schematic representation of the constitution of unmodified white noise (a), and of the effect upon its constitution of filtering it so that (b) an octave wide noise band, (c) a third of an octave wide noise band, and (d) a sixth of an octave wide noise band remain.

FIG. 4.—Masking effect (decibels rise in threshold of audiometer test tone) produced by various masking sounds upon a series of normal listeners, at various test-tone frequencies, and at the various sensation levels shown (decibels above the tested subjects' threshold for the masking sound). Masking sounds thus treated: (a) Zwislocki noises at 2000 and 4000 c/s, and third of an octave noise bands centred at 250, 500, 1000, 2000 and 4000 c/s. (b) Zwislocki noise at 500 c/s. (c) Modified mains hum on 1000 c/s. (d) Zwislocki noise at 1000 c/s, and modified mains hum on 500 c/s. (e) Zwislocki noise at 250 c/s. (f) modified mains hum on 2000 c/s. (g) Modified mains hum on 4000 c/s.

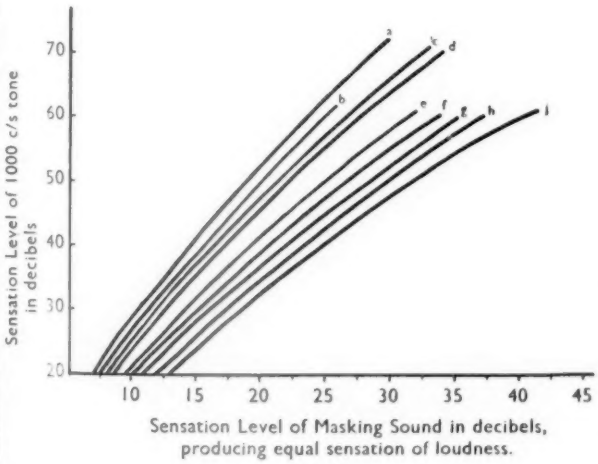

FIG. 5.

FIG. 5.—Loudness balance graph of results obtained with normal listeners, relating the sensation level (decibels above the tested subject's threshold) of a 1000 c/s audiometer test tone, to the sensation level to which various masking sounds must be raised in order that they may be of the same loudness as the 1000 c/s test tone (i.e. loudness of various masking sounds in Phons at various sensation levels). Masking sounds thus treated: (a) Modified mains hum, and Zwislocki noise at 250 c/s. (b) Third of an octave noise band centred at 250 c/s. (c) White noise. (d) Zwislocki noise at 500 c/s. (e) Third of an octave noise band centred at 500, 2000 and 4000 c/s. (f) Zwislocki noise at 1000 c/s. (g) Third of an octave noise band centred at 1000 c/s. (h) Zwislocki noise at 4000 c/s. (j) Zwislocki noise at 2000 c/s.

of extra apparatus. So far as simplicity in operation is concerned, it is merely necessary to know the hearing loss of the ear to be masked for the tone which is to be obscured. Supposing this hearing loss to be 20 db. and the masking effect required 30 db., then the masking sound attenuator must be set to the 20 + 30, that is, the 50 db. position. It is scarcely possible to devise any simpler method than this. The extra apparatus required is a gramophone reproducer which will replay recordings of the necessary third of an octave noises, plus an attenuator for the control of the intensity of the masking stimulus. It is felt that many hearing testing departments will already have a speech audiometer which will admirably serve the same purpose; in such a case the only additional cost will be that of the gramophone recording of the noises which we hope will be available in the near future. In the case of many pure-tone audiometers it will be possible for the manufacturers to incorporate this type of masking sound, the only additional expense being that of the record player.

As an alternative to the gramophone reproducer, it is possible to include a noise generator and the necessary filters in the pure-tone audiometer. In this event the audiometer control which selects the frequency of the test tone will, at the same time, select the correct masking noise band. The question of providing this added circuitory at low cost and without adding materially to the bulk of the pure-tone audiometer is at present being investigated. Information on these points, together with details of the electrical characteristics of the filters and other equipment used in these experiments, will be published in full elsewhere.

Summarizing the points we have attempted to make, these third of an octave bands provide masking sounds of high efficiency which are easily distinguishable from the test tone they are intended to mask. They are simple in operation and independent of the tested subject's type of audiogram, and last but not least, the necessary apparatus is simple to manufacture and can be incorporated at low cost in most commercial audiometers.

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Mr. A. Tumarkin asked whether it might not be more efficacious to use third of an octave noise bands centred at a frequency slightly below rather than at the test tone frequency.

In reply, **Mr. Denes** and **Mr. Naunton** agreed that such a measure would probably produce a masking sound of slightly greater efficiency, but as all the available noise filters centre at the customary round figure audiometer test-tone frequencies, and as any variation from this common practice would be more expensive, it was felt that the slightly less efficient compromise was justified.

The Comparative Anatomy of the Labyrinth

An Example of the Evolution of a Special Sense Organ

By OLIVER GRAY, M.D., Haslemere

OPPORTUNITY was given, at this meeting, of seeing a number of specimens illustrating the evolutionary stages in the development of the labyrinth or internal ear, commencing with the simple organ found in the Cyclostomes (Hag-fish and Lamprey), to the elaborate structures which exist in Fishes, Amphibians, Reptiles, Birds and Mammals. This makes a most fascinating study, for the story is a fairly complete one, and, incidentally, deals with the most beautiful entity in vertebrate anatomy. A glance at the photographs of the labyrinths of Man (Figs. 1 and 2) and of the Pig (Fig. 3) will abundantly support the latter contention. Such specimens require a certain amount of patience and skill to prepare, and are only obtained as a result of a process which takes at least three months.

A difficulty which often confronts the uninitiated lies in the significance of the membranous or otic labyrinth, as distinct from the osseous or periotic labyrinth which surrounds it and contains perilymph. The capsule, mostly bone, which enclosed the membranous labyrinth of the fish, invests the organ much more intimately in the amphibians, reptiles, birds and mammals; so that the semicircular ducts come to lie within the *semicircular canals*, the utricle and saccule within the *vestibule*, while the endolymphatic tube of the cochlea, called the *ductus cochlearis* or *scala media*, becomes surrounded, on either side, by the perilymph spaces known as the *scala tympani* and *scala vestibuli*.

Perhaps another helpful way of explaining how the membranous labyrinth comes to lie, more or less, suspended within the osseous labyrinth can be offered. In the human embryo the membranous labyrinth, ectodermic in origin, has almost completed its final shape by the 40 mm. stage. It is only now that rifts begin to appear in the surrounding mesenchymatous tissue. These rifts eventually coalesce to form the perilymphatic spaces which constitute the osseous or periotic labyrinth, the completion of which occurs about the middle of fœtal life.

It can be argued that the labyrinths of the hag-fish and lamprey do not represent an early stage in evolutionary development, but are degenerate forms of a more elaborate mechanism, which may have existed in earlier times. The cyclostomes are certainly very degenerate creatures in many respects, and it is curious that, being of the same family, their labyrinths are so dissimilar. This may, however, be accounted for by the fact that each has a distinct and ancient origin; each, as it were, with a long, independent twig coming from the Marsipobranch stem, very early in fish evolution. Again, the related fossil Cephalaspids, which are not supposed to be degenerate, had two semicircular ducts, like the lampreys (Stensio). Things must have their

beginning some time, and, as these fishes are primitive, it is fair to assume that we are, in fact, dealing with a very early stage in the history of the labyrinth.

It is my belief that the labyrinths of the skates and dogfish represent the highest perfection ever achieved in the labyrinthine mechanism that subserves the sense of balance and positional function. Thereafter, a less perfect organ proved adequate when augmented by a larger brain, correlating eye, muscle and joint sense. Why, for instance, should the semicircular canals, ampullæ, utricle and saccule be so much smaller in birds, whose movements in space are so much more rapid than those of the fishes?

In the skates and dogfish, the anterior and the posterior semicircular ducts each complete the circumference of a ring, and there is *no common crus*. From the anterior portion of the posterior duct, a canal, quite large in dogfish and small in skates, runs to the large saccule, which lies tucked up inside the semicircular ducts. The lower portion of the anterior duct is dilated to form the utricular recess. Presumably, the lateral duct arose from the anterior duct. Its ampulla lies adjacent to that of the anterior duct, and both open into the

FIG. 1.

FIG. 2.

Human Labyrinth. × 4.

FIG. 3.—Pig (*Sus scrofa*). × 4½.

Note on the Method of Preparing the Labyrinth, Processed by the *Paraffin Method* of the late Dr. A. A. GRAY, with Fin a Mounting in *Liquid Paraffin.*

This end modification (O.G.) is of significance. The end-result is permanent, and can be handled without fear of breakage. The paraffin wax cast of the labyrinth, obtained by the paraffin method, is suspended by means of a single strand of silk, unravelled from a silkworm cocoon. The tiny silk fibre is threaded through the superior or posterior canal (or both) and the ends secured, with Durofix, to the under surface of the lid of the future Perspex box, in which it will finally be mounted. This lid has previously had a tiny hole bored through it at one corner. A lidless Perspex box of appropriate size is filled three-quarters full with xylol, and the wax cast immersed in this until the paraffin is cleared (about forty-eight hours). It will now be seen that the periotic (so-called osseous) labyrinth is preserved, with the otic (membranous) labyrinth within it. In other words, the whole labyrinth (perilymphatic and endolymphatic) is complete. The final lidless Perspex box is now three-quarters filled with medicinal liquid paraffin, and the upper edges evenly spread with Durofix. The very delicate labyrinth, attached to its lid, is very carefully transferred from the xylol to the paraffin, and a weight placed on top of the lid. After twenty-four hours the box is completely filled with liquid paraffin by means of a 10 c.c. syringe, with a large bore needle, through the hole referred to, which is then sealed off with Durofix.

utricular recess, a relationship which persists throughout the subsequent history of these structures. The lateral duct sweeps outwards and then returns to the anterior duct, which it enters in the region of its posterior vertical limb; in so doing it runs within the arc of the posterior duct and, in this respect, differs from the state of affairs found in the bony fish (Teleosts). On the other hand, this is the condition found in amphibians, reptiles, birds and mammals, and, incidentally, also in that primitive Selachian, the *Chimaera monstrosa*. Several changes take place in the bony fish. *The adjacent portions of the anterior and posterior ducts come together and fuse to form the common crus.* In most instances the intervening membranous walls disappear, and the common crus becomes a single tube; but in some species the crus can be torn so as to split it into two parts longitudinally; and, again, a bubble of air will sometimes be seen squeezing its way up one side of the double-barrelled chamber. These observations both indicate a half-and-half stage in the formation of the common crus, for it is a single tube in amphibians, reptiles, birds and mammals. *The fusion of the two semicircular ducts thus brings about the formation of the utricle*, the anterior portion, largely composed of the utricular recess, coming from the anterior semicircular duct, the posterior limb owing its origin to the posterior duct.

The saccule lies dependent, below the utricle, with which it communicates by means of the same little canal which existed in the Elasmobranch, and which, now, can be given its appropriate title—the utriculo-saccular duct. The lateral duct has an interesting story. Its ampulla always remains adjacent to the anterior ampulla. In Elasmobranchs, as we have seen, its posterior extremity enters the descending posterior limb of the anterior duct. This point corresponds to a situation at the upper end of the common crus; in the Chimaera, which has a common crus, like the Teleosts, this end of the lateral duct enters the latter about half-way down the stem. By contrast, in the Teleosts themselves, it usually enters the posterior limb of the utricle, and, sometimes, as in the family Gadus, at a point at the extreme end of the chamber, very close to the posterior ampulla. In other words, *the posterior end of the lateral duct has "wandered" down the stem of the common crus, and then out along the posterior limb of the utricle.* Incidentally in certain families (Ostariophysi and Anarrhicas) there is a goblet-shaped dilatation at the junction, resembling that seen in 5% of human labyrinths, and in odd species like the Black-faced Kangaroo and the Marmoset.

One or two matters of detail together with a few brief observations are all that space allows. So far as I am aware these are original. One further point of major importance arises. It is possible that the labyrinth may prove to be a significant aid in the classification of species—greater, perhaps, than the teeth, which hitherto have made the largest contribution to this complex problem.

A British Medical Association scholarship has been a great help and encouragement to me in my work.

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Speech Audiometry: Its Value in Diagnosis and Prognosis

By Professor THEO. E. WALSH
Washington University, St. Louis

This paper will be published in the *Journal of Laryngology*

Section of Psychiatry

President—DESMOND CURRAN, F.R.C.P., D.P.M.

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DISCUSSION: PSYCHOSES IN CHILDHOOD [*Abridged*]

Dr. Mildred Creak:

Looking at the problem of psychoses in childhood, it is difficult not to be daunted by the terminology in the now quite extensive literature. One of the symptoms common to the group as a whole is singled out for attention, a new name is given, and it almost seems as if a new disease had been described.

For example dementia infantilis (Heller, 1908) suggests the early age of onset and the disintegrating course taken by the disease.

Hyperkinetic disease (Kramer and Pollnow, 1932) singles out the peculiar restlessness shown by these children, which is also of course described fully by Heller in his paper.

Kanner (1943) gives an excellent clinical description of wha *t*he calls Early Infantile Autism, stressing the fact that though his cases are not defective in the ordinary way, yet in this group an inability to relate themselves normally to the world around them characterizes these children from a very early age, if not even from birth.

It would seem much nearer the truth to regard the whole group of psychotic children as having one thing in common. They have arrived at their condition because they are all children to whom something has happened, sufficient to interrupt their normal development in every field.

The more closely the literature is studied, and it goes back to the middle of the nineteenth century, the more clear it is that children are not infrequently psychotic. The Luries' (1950) figure of 2%, found in the first 1,000 cases seen at a Child Guidance Home, probably gives an underestimate. Some of the children who would otherwise go to such a clinic will have already become quite unable to adapt themselves to ordinary life, and they will have been sent to hospitals for mental defectives rather than sent to a psychiatrist for diagnosis and therapy. It seems likely that a number of such children at an early age become indistinguishable from the psychotic aments. That the latter are not at all uncommon is a point which has not received the attention it deserved since Critchley and Earl (1932) drew attention to it in connexion with tuberous sclerosis.

If then we have a clinical grouping with certain features common to all, it is necessary to be clear as to which of these are essential to the diagnosis, and then to try by studying the whole child, his family, his nurture and all that has happened to him, to get nearer to what this common factor might be. For it is even not clear whether we are dealing with a genetic or a psychological or even a somatic common factor, although it is certainly true to say that some or all of these will be involved in the ætiology. If we think of these children as in some way especially vulnerable, sometimes to unusual traumata such as epidemic encephalitis, sometimes to very ordinary traumata such as the birth of a sibling, then we may be less bothered by the concept of numerous different diseases. We may even get somewhat nearer to understanding why these children fail to develop the normal patterns of defence, but instead go to pieces, continuing to function only in a fragmented and very peculiar way, for which Winnicott (1945) used the term "falling to bits" of the personality.

My aim in giving this brief introduction to the subject is to de-limit the field, and to clarify, and if feasible, unify somewhat the clinical picture. There is no need to spend time on those diseases where the ætiological factor is known, such as G.P.I. or epidemic encephalitis, although these, too, are conditions capable of causing psychoses in children. Even with the organic group, however, it is far from clear as to how the lesions described do in fact cause the results which we see reflected in the child's behaviour. In some other cases, mental changes appear to accompany a brain lesion rather than to arise directly as a result of brain tissue involved. This was the case with two intelligent children, one with moderate and demonstrable birth injury, the other with minimal signs of such, who both showed bizarre mannerisms, thought disorder and curious inhibitions suggesting a psychotic illness, which in one had existed, as far as one could see, from birth.

The problem of manic states and depressive states has been given more attention since Scott (1948) and other psychoanalysts have thrown light on the clinical disorders of a depressive kind in early childhood, and since Klein (1948) put forward the concept of the "depressive position" as a developmental stage in a child's emotional maturation. Here again, we shall find a merging that cannot be precisely delineated at the present time. In any case, so much of early childhood includes experiences which take place before integration is complete, that any disturbance, profound enough to shake the child's attachment to reality, will inevitably tend to produce a schizophrenic-like picture.

No attempt has been made to include in the group of psychoses under discussion any *separate* clinical pictures of manic-depressive states, nor have I attempted to include psychoses occurring, *for the first time*, at or around puberty, when the prevailing emotional instability tends to give a heightened effect which is confusing.

The syndromes which are left to be considered include major psychoses of early childhood such as the condition described in 1908 by Heller as dementia infantilis; the condition which Kanner has called early infantile autism, and which he believes is congenital but distinguishable from amentia; and the schizophrenic-like reactions with or without epilepsy, with or without physical signs, in which the prevailing disorder is seen as something more than can be accounted for by any actual lesions which can be demonstrated. In the majority of cases these early schizophrenic-like states show no physical signs or stigmata.

Broadly speaking, the psychotic illnesses occurring in early childhood before emotional organization is completed are more likely to cause a permanent disruption, with subsequent failure to resume the normal developmental pattern. These are the cases which "dement": some do deteriorate; others stand still for so long that they get left behind. In some the psychotic pattern appears to be present at birth, and undoubtedly some can only be regarded as psychotic aments. Because the illness is sometimes ushered in with ill-defined physical disturbances, or because of accompanying fits, it seems likely that a number of these early syndromes, dementia infantilis, dementia præcoxissima, pfropfhebephrenia—call them what you will—are organically caused, although no unequivocal morbid anatomy has yet been described.

After 5 years of age the child is better able to withstand the impact of such illness and between 5 years and puberty, some of the schizophrenic-like psychoses which occur, disappear partially or completely, although many carry a bad prognosis. Where an attack occurs in this way to a child whose previous personality appears to predispose him to it, the possibility of it being a recurrence after a long remission should be considered. Naturally, the more evident the psychogenic factors, the more likely it is that the diagnosis will be confused by a period of disturbed behaviour which can be regarded as a defence of the psyche against overwhelming anxieties and conflict. Indeed, the keynote to this illness is the child's inability to cope with his anxiety, and hence to tolerate any new situation which demands from him a need for new adjustments. As a group, the child psychotics resemble each other in many ways, of which this rejection of new situations is a striking example. It is much easier to recognize the psychotic child than it is to define the nature of his illness, although what is more characteristic of madness than its apartness and privacy? Even in the depressive adult patient, who has what we like to call full insight, the minute self-examination, the harsh standards of criticism and reproach all carry a self-imposed quality. "He can't be reasoned with", they say. This is more than ever true of the psychotic child whose actions are so hard to understand.

In the normal child, his close association with an adult, usually his mother, is very apparent. He looks out at the world from a sheltered position. He is warmly protected and so finds both the medium and the opportunity for striking his emotional roots. He relates himself to objects and to other people out of his primary experience of a safe love. It is as if, at this early stage, the external reality were judged in the light of past good experiences which have become internalized. The normal child, however individualistic he may be, is therefore not seen as an individual wholly separate from his environment.

In the psychotic child this linking to his family background is disturbed and altered. His unreal quality is apparent not so much in his judgments and in what he says, as in his detachment. He is uninfluenced by external reality, so that he lacks social awareness, or he is influenced in an unexpected

way personal to himself. Very often he ceases to communicate and speech either fails to develop, or deteriorates into fragmented and autistic usage—for example "there's the yellow air, the yellow air's a brick", as one such child remarked.

Another quality which we recognize in all psychotics, and which presumably relates to their autistic sense of values, is a tendency to inappropriate emotional responses. They may appear on the one hand indifferent, or on the other elated, or distressed and agitated, such reactions seeming to us irrelevant to their circumstances.

Yet another feature is a quality which for want of a better word I must call rigidity. An action, once started, continues indefinitely. Words, phrases, motor behaviour and even reaction patterns such as sleep and appetite tend to become stereotyped. An example of this was given by a psychotic child who liked chocolate but would only take it if cut in squares. Round chocolate croquettes he would reject.

The normal child progresses, and his pattern of behaviour evolves, while the child psychotic is reminiscent of a gramophone needle which has become stuck in a groove on the surface, and so goes on and on playing the same notes. Because of this, they seem boring and unresponsive, and there is a dangerous (almost inevitable) tendency in those who live closest to these children to fall in with the rigidity, especially when departure from routine may provoke such unpredictable, and often severe, reactions.

Kanner (1943) and others have noted that the parents of these children are over-intellectual or somewhat aloof, and sometimes themselves obsessional. But a mother's maternal capacity blossoms in response to a demand, and the quality required by these mad children is tolerance coupled with detachment. Such an attitude may, however, even become a defence on the part of the parent, against the frustrating exercise of trying to love the child and at the same time trying to maintain some contact with his mental processes. It is easy to see that this attitude of defence, if it does become established, will then militate against both normal affectionate relationships, and intellectual progress which in the young child depend one on the other. If, however, the psychotic child with a schizophrenic-like illness were wholly the product of his nurture, it might be more common than it is to find two such children in one family.

Bender (1947) makes the point that the impact of this illness cuts across every aspect of the child's development, and the apparent deterioration of many cases may be partly a true regression. Reaching a standstill, however, also means that essential stages are never reached, or are by-passed, as in the children who acquire uncanny motor skill but never communicate in speech. Thus, a child unable to feed himself or dress himself will balance on a narrow wall or twiddle a tin lid with fascinating dexterity. But his skill remains unrelated to any purpose, or to any feeling between himself, his setting, and the thing he is playing with. Furthermore, since the position of an organism so disintegrated is of itself a source of anxiety, the odd imperfections in perceiving the world around him, and in self-awareness, may impart a terrifying sense of difference to the child, which in turn he can neither communicate nor rid himself of.

A film was shown to illustrate these points:

Case 1.—Boy, aged 14, eldest of 3, with normal early development who became ill aged 2½, when he "suddenly" ceased to talk, and regressed in his habits. His actions became repetitive with considerable disturbance at night, and with increasingly impulsive behaviour. Speech is limited to cries or calls, there are no physical signs in the C.N.S., and his physical development, though nutritionally adequate, shows no secondary sexual characteristics.

He was shown sitting in a chair, rocking to and fro, grimacing and pulling a woollen scarf off and on in a repetitive manner. The observer was seen to ask him for the scarf and hold out her hand towards it. This simple action threw him into excited negativism, crying, howling, clutching on to his scarf with more violent rocking. Then the film showed that he acceded to a repeated request for the scarf, which he gave up without protest or real interest in retaining.

Case 2.—Boy, aged 5, only child, with normal early development whose illness began suddenly, aged 4½, with bad sleep, physical restlessness, talking to himself, loss of toilet control. All symptoms had become much worse following a short (three weeks') hospitalization, when all physical findings were negative.

He was shown playing in a monotonous way with a wooden skittle and a small tin, banging one on the other. Facial grimacing went on all the time and he disregarded the observer. When she removed the skittle and "hid" it inside the tin, he continued his play without it and was some time before he resumed hold of it. He lost interest altogether when it was held out to him at a lower level, so that he had to stoop to reach it. He was seen to be talking to himself throughout this play.

Case 3.—Girl, aged 4, middle of 3, quiet good baby, "taught to speak" aged 3½. Motor development also a little late by average standards. At 13 months noted "not interested in people, only in things". Became disturbed at night, with regression in habits. Onset insidious, and perhaps associated with birth of sibling, perhaps with severe eccentricities in parents leading to constant disagreements. The film was taken during a short hospitalization, during which she had been observed to become less withdrawn. She was shown seated on a cot beside observer. She tolerated an affectionate supporting arm, but turned away from observer's

face. She drew back from a proffered pencil, and proffered toy, and throughout the film, momentary stereotyped postures, and finger play were visible. Her expression remained somewhat blank and always unhappy and puzzled. She held on to observer's hand, although making no use of it; when the hand was withdrawn, she tottered a little towards it, as if indicating a need for support (although she stands and walks perfectly by herself), but made no active protest or effort to regain this support. Her passivity persisted in spite of several proffered toys, all of which she was known to like as playthings.

Case 4.—Boy, nearly 10, only chil ¢but mother a war widow. Early development a little slow but speech "clear and definite" by the age of 2. Became ill in his fourth year, when first noticed to be limiting use of speech to verbal repetitions. Had many obsessional demands, e.g. knife, plate, fork to be placed only in certain positions. Sleep became bad, habits regressed, until now is mute, very restless, places everything in his mouth. Film showed a labile, fatuous expression, with a withdrawn and "faraway" look. He repeated a number of curious, but highly co-ordinated repetitive movements with bricks, touching them, pressing them and touching his mouth repeatedly in an exactly similar ritual. He appeared oblivious of the observer, and continued without protest at interruptions deliberately made by her.

We thus come to understand a little of the aloneness and extreme self-centredness, of inappropriate and unpredictable emotions, and of the rigid and stereotyped and ultimately limited pattern of response so characteristic of the psychotic child.

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Dr. G. O'Gorman:

The greatly increased attention which has been paid recently to the subject of childhood psychosis has prompted some pertinent questions from one's medical colleagues; for example: "What happened to all these children in the past?" and "Why haven't we seen them?"

The answers to these queries, which are suggested in the light of recent experience in Mental Deficiency Hospitals, are as follows: A few of them remained at home; a rather larger number went to Mental Hospitals; and the vast majority were admitted to Mental Deficiency Institutions where they usually stayed, though some were later transferred to Mental Hospitals. Thus doctors who did not work in such institutions did not see them.

For this state of affairs there are three main reasons—pathological, legal and practical.

In the first place, the nature of psychosis in childhood—just like untreated schizophrenia in the adult—is that, whereas in a few cases spontaneous recovery occurs, in others there are relapses and remissions, and in the majority the process continues until a state of dementia is reached; the degree of dementia depending on the duration and severity of the psychotic process. Now, what is the effect of a dementing illness on a growing mind? It is as though a child who was being carried steadily upwards on the escalator of normal mental growth were to turn round and begin running downwards. If he runs slowly, or only for a short while, the escalator must still carry him upwards, but when the escalator stops, at the age of about 16, that child will be much lower in intelligence than those whom the escalator has carried upwards in the normal way. Before that age, it is suggested, psychosis tends to result in retarded mental growth. Thereafter, it produces deterioration and dementia. Where the psychosis begins early and deterioration is considerable, then the child demented as a result of his psychosis will be hard to distinguish from the true ament. For this reason, it is not surprising that many childhood schizophrenics reach the mental deficiency (M.D.) colonies.

Secondly: the legal definition of mental defect is "arrested or incomplete development of mind, existing before the age of 18 years, whether arising from inherent causes or induced by disease or injury". We are in some doubt as to whether these psychoses of childhood arise from inherent causes, or are induced by disease. But they must arise from one or the other; and, if it is agreed that schizophrenia in childhood can arrest development of mind, then the legal implications are plain: namely, that every schizophrenic whose disease began before the age of 18—possibly 75% of the total—is mentally defective. The M.D. colony is therefore, legally, the right place to send these young psychotics.

The third reason why psychotic children are found in M.D. colonies is, of course, that there is nowhere else to send them.

Diagnosis.—On the subject of diagnosis the question is often asked: "How can the young schizophrenic be distinguished from the ordinary mental defective?" By "ordinary mental defective" most people mean one in whom an organic cerebral process is responsible; whereas a schizophrenic would be regarded as one in whom the process is in part constitutional and in part reactive. But any brain-injured child tends to be more defective as a result of the psychological sequelæ of his basic defect—thus a boy with a specific verbal disability who cannot understand what is said to him not only fails to develop his inherent abilities through lack of teaching, but may also become withdrawn and seclusive or apathetic, and thus appear even more defective. On the other hand, most people admit that schizophrenia has some constitutional predisposition—and surely that must have a physical basis. One is more and more convinced of the importance of constitutional predisposition because some of our children appear to have been psychotic from birth, but do not appear to have any of the usual features of organic disease of the central nervous system. The problem is further complicated by the description of cases which are found at autopsy to have been suffering from organic conditions such as tuberous sclerosis, but whose symptoms during life had been very similar to those of children in whom no organic disease could be detected.

Further difficulty in diagnosis arises from the fact that an ament of subcultural type may become psychotic, yet among mental defectives I have seen it would, I feel, be less true to say "psychosis frequently supervenes in the ament" than it would be to say "psychosis is a common cause of mental deficiency".

In the past, when a simple schizophrenic process has begun early, the child has been diagnosed as a mental defective. When florid schizophrenic symptoms developed later a change of diagnosis had to be made, thus fostering the idea that the subcultural defective is especially liable to psychosis.

With these reservations we may attempt to indicate what seems to be among the most helpful diagnostic criteria:

(1) *Family history.*—Most types of mental defectives tend to have a family history of defect; the juvenile psychotic does not. His family history is that of the schizophrenic—eccentricity, alcoholism, neurosis, instability and occasionally psychosis. One very frequent, though by no means constant, finding has been that the mother is a person who lacks emotional warmth for her children, or at any rate for this child. In other cases there is rejection of the child, conscious or unconscious, from the time of its conception; or the mother has been subjected to severe strain during pregnancy, or the puerperium. In many of the cases we are seeing now there was considerable mental or physical stress due to the war (bombing, separation of parents, mother working, or bereavement) but it is not possible, so far, to decide how much special effect such factors may have had.

(2) *Personal history.*—If the parent says "he was perfectly all right until . . . " (some age, usually about 4 or 5, when the deterioration began), then psychosis must be a likely diagnosis, unless there is a story suggestive of cerebral infection or injury around that time.

A previous history of fits does not necessarily preclude a diagnosis of schizophrenia because one sees patients who have a story of fits between the ages of about 5 and 10 years with subsequent cessation of attacks followed by psychotic deterioration later on. As against the contention that "fits mean an organic process and rule out schizophrenia" is the work of Dr. Denis Hill who has shown how convulsive attacks with epileptic types of EEG occur in schizophrenia.

(3) *On examination.*—One must not be deceived by the appearance of the child. When these children are seen at the Child Guidance Clinics they do not look like defectives. They are intelligent in countenance. Their movements are graceful and well co-ordinated. They do not have the dull appearance of the mentally defective. That is true, but only of the early case whose parents are intelligent enough to take him to the psychiatrist. The deteriorated childhood psychotic looks like everybody's idea of the mentally defective. In the earlier stages the attitude may be characteristic. The head tends to be rotated a little and to sit at an odd angle on the shoulders, which may themselves be unevenly disposed. The hands, in repose, are held in odd positions, perhaps with the fingers at different angles and the wrists unduly flexed. They may sit for long periods with the trunk bent forwards or sideways in seemingly uncomfortable postures, with the legs similarly disposed. The expression is often peculiar, and grimaces are not unusual as the condition progresses. Pulling the lips up into a snout, narrowing the eyes, or looking upwards and sideways, are the types of facial mannerisms seen.

An important feature is partial preservation. They may retain their skill in manipulation or their musical ability—one patient can still play the piano—or their ability to eat daintily. Sometimes they can even be taught little handicrafts although the mental age on testing would be several years below that at which such skills are learnt.

Routine schizophrenic symptoms are of course common: causeless laughter, excitement, impulsiveness, obvious hallucinosis, attitudes, all these may be seen but of course they are rare in early cases.

The fundamental change to be concentrated on in diagnosis surely is that, for these children, the meaning of reality is different. Their contact with the real world appears purposively limited. Toys, for example, they either ignore or manipulate inappropriately. Many sensory stimuli they will reject—cold, for example, or pain. Yet they frequently seek sensual gratification—some love to feel smooth surfaces, one likes to rustle crinkly paper, another would pour water into a tub all day, or let soil trickle endlessly through his fingers; most of them masturbate. They enjoy physical exercise but it is not normal exercise: it is rocking; odd jumps into bizarre attitudes; head banging—oblivious of the pain. One child, who could walk normally, preferred to slide himself along on his seat. Some of them like to spin around or to run round in little circles.

In those who have not deteriorated too far symptoms may be seen which smack of the obsessional; an endless pulling up of socks, for example; arranging everything in straight lines; an extraordinary distaste of having a single speck of dirt on them. (One case, who showed this symptom, also had fæcal incontinence.) Some of them will go to any lengths to avoid unpleasant smells or distasteful noises.

As to speech, they mostly have a history of developing normally up to a stage, then silence. But many of them can speak if they will. Some of them will only echo the words of others, while some make odd, complicated noises which seem to be a sort of imitation of real speech. One 10-year-old boy, after a silence alleged to have lasted for years, picked up my propelling pencil and said: "These pencils unscrew, you know." He then relapsed into silence and I never heard him speak again. However, he retained my pencil. But he does not use it to scribble with. He sits drawing its smooth surface back and forth across his upper lip.

Most important of all, human relationships are altered. But they exist. One boy, for example, who is 13 years old, has to be approached and made a fuss of as soon as the doctor enters the ward. If not, he will kick one of the other children on the shin. The other day I witnessed the leave-taking by her mother of a psychotic girl. The girl is now aged 11; the mother was going abroad for a long absence and she had tried to convey this to the child, who had not spoken a word during the visit. The mother was in tears; the girl looked at her without expression, then turned to the nurse and said: "Bed-time." And yet, two days before that, the same child broke off one of her solitary games to walk up behind one of the nurses and kiss her. For the next week she completely ignored that nurse.

This alteration in human relationships is, I believe, the key to the approach to these children. Perhaps if one gets them before they have deteriorated too far, and persuades them to establish a loving relationship with one human being, then I believe there is some hope for some of the cases. And it is in this direction that we at Henley are directing our efforts.

Dr. D. W. Winnicott:

In the third contribution to the discussion[1] Dr. D. W. Winnicott developed the theme that some degree of psychosis in childhood is common, but that it is not noticed because of the way in which the symptoms are hidden in the ordinary difficulties that are inherent in child care. According to this theory the diagnosis is made only when the environment fails to cope with the distortions of emotional development, so that the child needs to organize along a certain defensive line which becomes recognizable as a disease entity. The theory is based on the assumption that the basis of the mental health of the normal individual is laid down in earliest infancy by the techniques which come naturally to a mother who is preoccupied with the care of her own infant; in the same way neurosis is prevented only by a natural and reliable management of the first interpersonal relationships. Dr. Winnicott made a brief sketch of the tasks involved in the early stages of the emotional development of the infant, tasks which cannot be achieved without an emotional environment that is good enough.

[1] To be published *in extenso* in (1953) *British Journal of Medical Psychology*, **26**, Part 1.

Section of Endocrinology

President—A. W. SPENCE, M.D., F.R.C.P.

[*May* 28, 1952]

JOINT MEETING WITH THE SOCIETY FOR ENDOCRINOLOGY

The Endocrine Treatment of Dysmenorrhœa

By P. M. F. BISHOP, D.M., M.R.C.P., and EDUARDO ORTI, M.D.

THERE is considerable difference of opinion concerning the incidence and severity of dysmenorrhœa. According to Ingersoll (1947) the incidence is 34%. Drillien (1946) found dysmenorrhœa interfering with routine duties in 23% of a series of women serving in the A.T.S. Hamblen (1945) recorded dysmenorrhœa in only 6–12% of women college students. Davis (1938) noted that 1 to 5% of his series of women were incapacitated by dysmenorrhœa. Emge (1933) analysing 4,500 consecutive gynæcological patients found that 2·8% described dysmenorrhœa as a symptom. In 1945 a questionnaire was sent by one of us (P. M. F. B.) to the nursing staff of Guy's Hospital, Chelsea Hospital for Women and the R.A.F. with the approval and kind permission of the Matrons of the two hospitals, the Matron-in-Chief of the R.A.F. and Air Vice-Marshal Sir Harold Whittingham to whom our grateful thanks are due, as well as to the nurses answering the questionnaire. 16·5% of 472 complained at some time of incapacitating dysmenorrhœa (i.e. with pain so severe as to necessitate lying down or abandoning work). 16·8% of these 472 nurses recorded menstrual irregularity at some time, and the incidence of incapacitating dysmenorrhœa was 25·6% in those with irregular cycles as compared with 15% of those with regular cycles. This suggestion of "menstrual instability" being associated with a tendency to dysmenorrhœa is strengthened by the observation that there was a greater "scatter" in the age of menarche in 330 patients complaining of dysmenorrhœa than in 466 nurses who did not experience painful periods (Fig. 1).

The wide discrepancies recorded by different observers as to the incidence of dysmenorrhœa are possibly due to their approach to this condition. Hamblen (1945) for instance says: "Many of the patients are addicted to bromides and barbiturates . . . The physician should never be a party to starting the drug habit . . . The patient should be told frankly that the more sedatives she takes, the more her tolerance to pain is lowered. Acceptance of menstrual discomfort should be urged and no hope for euphoric genital bleeding should be extended . . . Data on the absenteeism of industrial workers because of dysmenorrhœa are unreliable since menstrual discomfort affords a convenient excuse"; and expresses the opinion that "few, if any, healthy sexually adequate and psychosomatically sufficient women have dysmenorrhœa". Others are strongly in favour of taking active, and even drastic, steps to relieve the condition. Davis (1948), for instance, holds the view that "the operation (of resection of the presacral nerve) is curative in cases of severe spasmodic dysmenorrhœa, and is indicated in those patients who remain unrelieved by medicinal treatment, cervical dilatation and alcohol injection". The truth probably lies between these two extremes. The psychogenic factor may indeed be important but there are cases which do not respond to common-sense psychotherapy. Dilatation of the cervix seldom abolishes the pain permanently, and frequently is completely without effect. On the other hand, many gynæcologists hesitate to undertake presacral neurectomy. Endocrine therapy is therefore forced to play a prominent role in the management of cases of incapacitating dysmenorrhœa. The gonadotrophins and all the sex hormones have been given a trial with variable success. Consideration of the many reports (Bishop, 1950) has led us to the conclusion that the only certain way of relieving pain in cases of true spasmodic dysmenorrhœa is to inhibit ovulation. Sturgis and Albright (1940) suggested that spasmodic dysmenorrhœa occurs only in ovulatory cycles, and is associated with the presence of an actively secreting corpus luteum. We have noted on many occasions that administration of progesterone has been followed by painful bleeding in patients who have not previously complained of dysmenorrhœa. Ovulation may be inhibited by giving œstrogen in doses of 2 or 3 mg. of stilbœstrol daily for fourteen days commencing within five days of the onset of the previous menstrual bleeding. This is the thesis on which the present studies are based.

1,300 case histories of patients attending the Endocrine Clinics at Chelsea Hospital for Women and the Gynæcological Department at the Postgraduate Medical School of London were analysed. 330 patients (25·5%) complained of incapacitating dysmenorrhœa, though this was the presenting symptom in only 185 (14·2%) of the cases. Of these 330 patients, 73 were treated with œstrogen: 945 menstrual cycles were charted, in 631 of which œstrogen was administered. 295 cases were analysed in connexion with the onset of dysmenorrhœa in relation to the menarche. It has been suggested that during the early months, or even years, of menstrual life the cycles are non-ovulatory and that therefore the onset of spasmodic dysmenorrhœa may be delayed until later in adolescence. In this series 158 (53%)

experienced dysmenorrhœa either at the first period or during the first few months, whereas 137 (47%) developed painful periods during adolescence or later. In 155 cases other menstrual disorders were also noted. 40 (26%) complained of excessive bleeding. In 35 (23%) there were phases of amenorrhœa exceeding a year, and in another 51 (33%) there was a history of irregular periods or oligomenorrhœa. 10 cases (6·5%) complained of premenstrual symptoms.

In view of Sturgis and Albright's contention that true spasmodic dysmenorrhœa occurs only in ovulatory cycles 148 cycles were studied using basal temperature records to determine whether ovulation had taken place. 87% showed the expected result, namely that the cycle was non-ovulatory and painless or else ovulatory and painful.

Many of the reports dealing with endocrine therapy in dysmenorrhœa record results in only one or two cycles. It has been our experience that the first two or three cycles tend to be painless whatever treatment is employed. We believe that these patients, far from being neurotic, are intensely anxious to be cured, and that therefore any new therapeutic regime or any new doctor will renew their faith in the possibility of cure, but that after a few months during which they have become accustomed to yet another form of palliative treatment any psychotherapeutic effect of the regime diminishes. Thus in order that the true effect of endocrine therapy may be accurately assessed it is necessary to study the response of the patient over a relatively long period of time. For this reason we have selected 27 patients in whom we have studied an average of 20 cycles, of which an average of 13 cycles have been treated with œstrogen. In no case have less than 9 cycles been œstrogen-treated. In this series 533 cycles have been charted, in which œstrogen has been administered in 356. No treatment was given in 158 cycles, and control (inert) tablets were prescribed in 19. The results of the œstrogen-treated cycles are shown in Fig. 2. They are arranged in order of descending dosage when given early in the cycle, and then

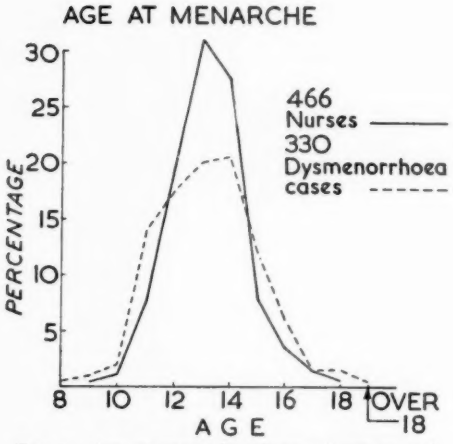

FIG. 1.—Age at menarche of normal nurses and patients complaining of dysmenorrhœa.

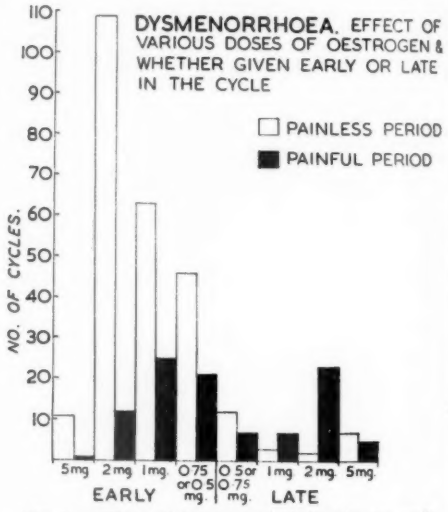

FIG. 2.—Effect of dosage and timing in the cycle in œstrogen therapy of dysmenorrhœa.

ascending dosage given late in the cycle (i.e. seven days or more after the first day of the previous period). These results seem to suggest that any dose of œstrogen equivalent to 2 mg. of stilbœstrol or more, given early in the cycle will frequently be followed by a painless period.

Many of these 27 cases have been studied for more than two years. The question arises as to whether prolonged œstrogen therapy of this nature may not be harmful, inasmuch as it may eventually induce permanent inhibition of pituitary gonadotrophic activity leading to ovarian deficiency and failure to produce ovulation. (It is important to ensure that at least a week's interval intervenes between successive courses of œstrogen.) This has been carefully studied by us and we have not yet encountered a case in which basal temperatures and recurrence of pain did not always indicate that normal, and painful, ovulatory cycles reappeared as soon as treatment was discontinued.

Thus we submit, from these observations, that it is possible to inhibit ovulation by giving 2 mg. stilbœstrol daily for fourteen days commencing within five days of the first day of the previous period, and that this almost always is followed by a painless "period" (œstrogen withdrawal bleeding). This treatment is palliative, but not curative, for even after two years, if it is discontinued, painful ovulatory cycles are likely to recur.

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Further Observations on the Chromatography of Urinary Gonadotrophins

By A. C. CROOKE, M.D., and W. R. BUTT, B.Sc.Lond., A.R.I.C.

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THE mouse uterine assay is a convenient routine procedure for urinary gonadotrophins in non-pregnant women and in men, but it does not differentiate adequately between follicle-stimulating and luteinizing hormones. The separation of these substances by a chromatographic procedure has been attempted and the method described in a previous communication (Butt and Crooke, 1952).

Briefly, the urinary gonadotrophins were extracted by the kaolin adsorption technique (Dekanski, 1949) and then fractionated by chromatography on tri-calcium phosphate columns (Swingle and Tiselius, 1951). The eluting agents were 0·002 M Na_2HPO_4 followed by 0·02 M Na_3PO_4. The eluates were assayed by the mouse uterine weight method (Levin and Tyndale, 1936) or by the rat prostate method (Loraine, 1950). The material eluted by Na_2HPO_4 will be referred to as gonadotrophin "A" (GA) and that eluted by Na_3PO_4 as gonadotrophin "B" (GB).

It was found that the biological activity was present in high concentration in GB and in low concentration in GA during pregnancy. At least 80% of the total gonadotrophins in three different specimens of urine from pregnant women occurred in GB. During the normal cycle, in functional amenorrhœa and after the menopause, however, the biological activity was mainly confined to GA. Activity was detected in GB during a brief part of the luteal phase of several normal cycles, and in the urine of one patient aged 26 years with functional amenorrhœa, who normally excreted large amounts of total gonadotrophins. Activity in GB also occurred in some specimens from women past the menopause. These findings suggested that GA may contain follicle-stimulating substances and GB-luteinizing substances.

In our subsequent work successive 3 ml. fractions of the eluates have been examined by the ninhydrin reaction for free amino nitrogen (Moore and Stein, 1948) and by the orcinol reaction for hexoses

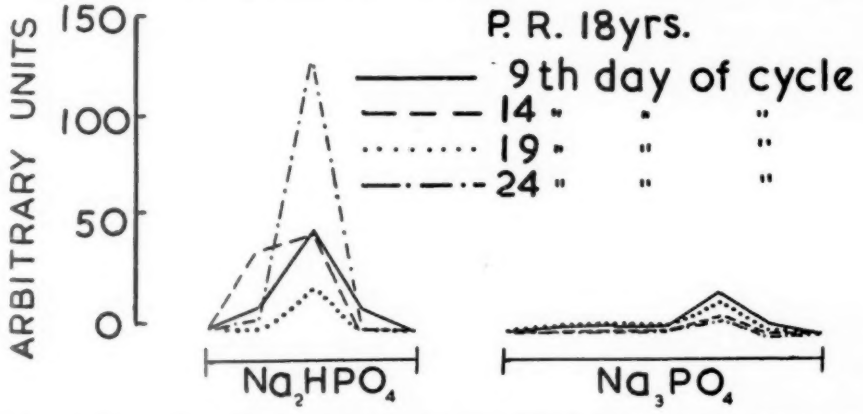

FIG. 1.—Chromatograms of urine collected during a normal menstrual cycle. Ninhydrin measurements of Na_2HPO_4 eluates. Orcinol measurements of Na_3PO_4 eluates.

(Rimington, 1940). The reason for employing these two procedures was that according to Li (1949) free amino groups are essential for the biological activity of pituitary follicle-stimulating hormone and interstitial cell-stimulating hormone, but are not essential for the activity of chorionic gonadotrophin. The ninhydrin reaction, therefore, may not measure chorionic gonadotrophin but all these hormones contain hexose and should give the orcinol reaction.

The results obtained by the ninhydrin method were found to give a fairly good index of the biological activity of GA but not of GB. The activity of GB corresponded more closely with the orcinol measurements. Both reactions were carried out on all eluates but for the sake of clearness the chromatograms shown in Figs. 1 to 4 represent only the ninhydrin reaction for GA and the orcinol reaction for GB. The figures were obtained on 100 ml. of night specimens of urine. This introduces an error owing to the great variation in the concentration of the various samples of urine but it was more convenient than using specimens collected over specified times for these preliminary investigations.

Fig. 1 shows the chromatograms of 4 specimens of urine obtained at different stages of a normal cycle. In each case the GA content is relatively high and the GB relatively low but an insufficient number of samples has been examined to recognize any characteristic pattern.

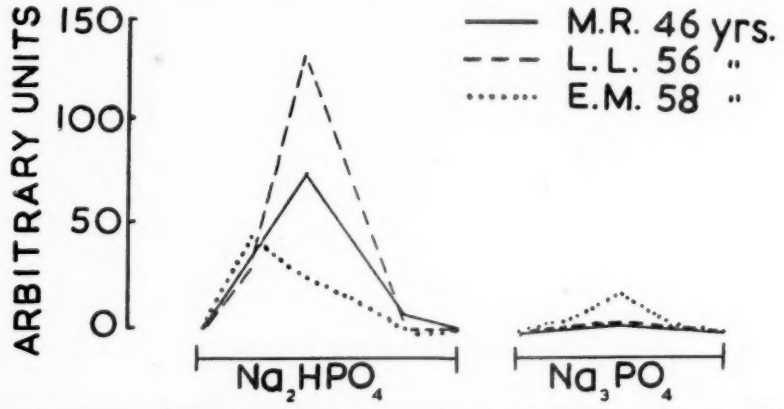

FIG. 2.—Chromatograms of urine of women past the menopause. Ninhydrin measurements of Na_2HPO_4 eluates. Orcinol measurements of Na_3PO_4 eluates.

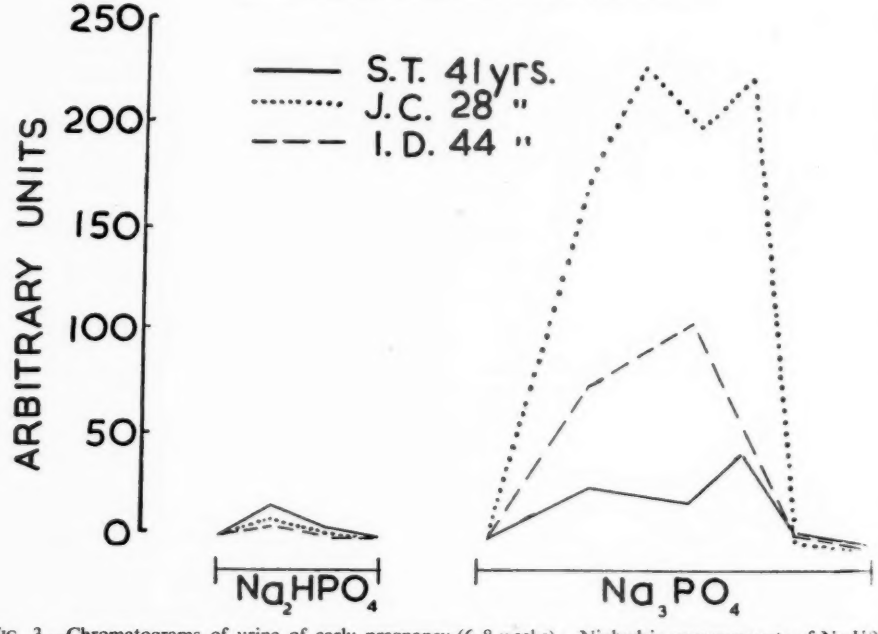

FIG. 3.—Chromatograms of urine of early pregnancy (6–8 weeks). Ninhydrin measurements of Na_2HPO_4 eluates. Orcinol measurements of Na_3PO_4 eluates.

Fig. 2 represents the chromatograms of 3 specimens of urine from women past the menopause. The patterns are similar to those of Fig. 1.

The chromatograms from pregnancy urine are shown in Fig. 3. Here the GB readings are relatively high and GA relatively low.

The chromatograms of 2 urines from women with functional amenorrhœa (Fig. 4) show fairly low responses with both ninhydrin and orcinol. One patient was treated with 1,000 units of a chorionic gonadotrophin preparation (Antuitrin S) and her chromatogram shows a high GB fraction with orcinol and resembles a pregnancy chromatogram.

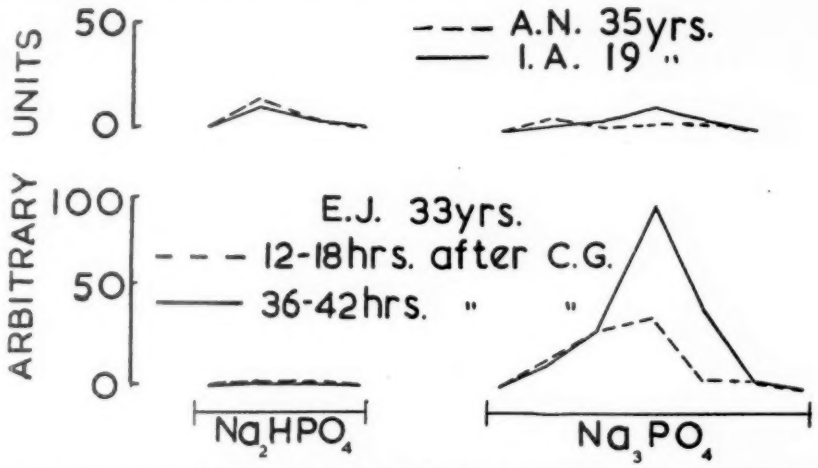

FIG. 4.—Chromatograms of urine from women with functional amenorrhœa. (*above*) Untreated. (*below*) Treated with 1,000 international units of chorionic gonadotrophin (Antuitrin S). Ninhydrin measurements of Na_2HPO_4 eluates. Orcinol measurements of Na_3PO_4 eluates.

It will be seen that the results of the chemical analysis correspond with the biological findings. In each case GA is high in the normal cycle and the menopause, and GB is high in pregnancy and after the administration of chorionic gonadotrophins. We have not yet demonstrated any separation of follicle-stimulating and luteinizing substances biologically but investigations are in progress to establish this with hypophysectomized rats. The contrasting chromatographic patterns in these different conditions lead one to hope, however, that by the selection of suitable reagents it will be possible to develop a chemical test for the diagnosis of pregnancy. Moreover the procedure may be applied for the measurement of the relative concentration of the gonadotrophins.

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Steroid Metabolism and Clinical Endocrinology

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ALMOST two thousand years have passed since Celsus suggested a correlation between arthritic disease and reproductive function. Here was an important clinical observation, with, as we now know, a possible therapeutic application, but further development of the theme was prevented by lack of knowledge of the underlying physiology and pathology.

As interest in the disorders of the endocrine glands has increased, so this lack of knowledge has

become ever more apparent, but elucidation has to a great extent awaited advances in mathematics, physics and chemistry. The present century has seen spectacular advances in organic chemistry—including the isolation, identification and partial synthesis of a group of phenanthrene derivatives—the steroids—and, furthermore, the recognition that many of the active principles secreted by the endocrine glands fall within that group. Already, significant progress has been made in the study of the biochemistry of the steroid hormones and of their metabolic products. As this new field is developed the clinical endocrinologist and the biochemist must join in an attempt to bridge the gap between the results of these basic studies and the solution of urgent clinical problems. It may be that the extent of this gap is not clearly appreciated and yet it must be apparent that a host of untested assumptions are involved in almost all attempts to derive diagnostic or therapeutic implications from existing experimental data. It is not enough to hope that the advancing frontier of science will overtake the ever-widening horizon of clinical medicine. Positive action must be taken to bridge the gap in certain areas.

It may be timely, therefore, to consider the types of study which are in progress in steroid biochemistry with respect to their applicability to the needs of the clinical endocrinologist.

For the purpose of discussion these may be divided into two categories.

(1) *Urinalysis for steroids of endogenous origin.*—In this type of study, no steroid is administered and the steroid pattern in the urine reflects the endogenous secretion of the parent hormones. It is obvious that the scope of such work is seriously limited by lack of knowledge of intermediary metabolism. Thus it is probable that too many biochemical changes intervene between the moment of secretion of the hormone and the urinary excretion of a metabolite to merit the deduction of the amount of hormone secreted from a knowledge of the amount of metabolite excreted. None the less, such information may be of real diagnostic or prognostic value. The physician is familiar with the usefulness and limitations of quantitative urinalysis for the presence of the neutral 17-ketosteroids or of the progesterone metabolite, pregnanediol. There is great need for improvements in methodology—notably in the specificity of methods for the determination of steroids of adrenocortical origin and the sensitivity of methods for the determination of the urinary œstrogens.

An advance of especial interest to the clinical endocrinologist has resulted from the application of infra-red spectroscopy to this problem. Using this technique, Dobriner and his colleagues (Dobriner, 1951) were enabled to study steroid patterns in greater detail and observed qualitative and quantitative differences in the excretion of individual steroids in groups of human subjects in health and disease. Thus, one steroid, 11-hydroxyetiocholanolone, is excreted by a significant number of patients with adrenal hyperplasia or neoplastic disease. Similarly, another compound—17-hydroxypregnanolone—was isolated from the urine of certain cases of rheumatoid arthritis and consistently from the urine of patients with adrenal hyperplasia (Dobriner *et al.*, 1951). This steroid was isolated from the urine of human subjects receiving the adrenocorticotrophic hormone, but was not detected in the urine of any of 28 healthy subjects. These observations led Dobriner to conclude that, in the cases of neoplasia or arthritis which were investigated by his group, there was abnormal adrenal function or, alternatively, altered metabolism of the adrenocortical hormones. The fact that these abnormal metabolites were excreted in the urine of patients with adrenal hyperplasia and, after stimulation of the adrenal cortex, appeared to favour location of the disorder in the gland itself.

(2) *Attempts to study the intermediary metabolism of the steroid hormones.*—In these studies an attempt is made to elucidate the manner in which the steroid molecule is handled by the cell, the organ or the total living organism. Thus information is obtained from *in vitro* experiments with homogenates and tissue slices, from the perfusion of isolated glands or target organs and from metabolic studies in animals and in the human subject.

The *in vitro* and perfusion studies are yielding information of great value concerning the metabolic changes which are likely to occur, and appear to offer the most promising route to an understanding of the chemical basis of the biological action of the steroid hormones. They are exemplified by recent work on the metabolism of the C_{19} steroids by individual tissues (Samuels, 1950, 1952) and by the studies of Pincus and his colleagues who use perfusion techniques to unravel the complexities of steroid biogenesis (Hechter *et al.*, 1951).

The investigation of steroid metabolism in the total living organism is of especial importance since evidence may be obtained indicating which of the probabilities suggested by the *in vitro* or perfusion studies actually occur. It must be recognized, however, that the study of steroid metabolism in the human subject is at a very early stage of development. Quantitative methods of urinalysis are still imperfect, it is difficult to assess the amount of steroid to which the organism is likely to be subjected under physiological conditions, the efficiency of absorption of the administered steroid is an important variable and ideal clinical material is rarely available. Frequently the choice lies between the healthy animal and the diseased human subject. Experiments are reported in which what appear to be very large amounts of steroid are administered to patients in the terminal stages of some chronic disease. The physician may well be baffled by data which emerge from this interplay of pharmacology and pathology. Despite these difficulties of technique and interpretation much has been learned from studies in which a steroid hormone is administered and the urine is analysed for a suspected metabolite. These advances have been reviewed elsewhere (Lieberman and Dobriner, 1951). Further progress in this phase of the work should result from studies with isotopically labelled steroids (Gallagher *et*

al., 1951). But it will be apparent that the main factor limiting their scope is the fact that the data are derived from urinalysis and that consequently the light shed upon the processes of intermediary metabolism is somewhat indirect. For this reason attention has been turned to methods for the quantitative determination of steroids in the blood or tissues of the body itself.

A high degree of sensitivity and specificity will be required of such methods but that the task may not be impossible is shown by the development of such a method for the quantitative determination of progesterone in peripheral blood (Butt, *et al*, 1951) and of a method for the quantitative determination of circulating 17-hydroxycorticosteroids (Nelson and Samuels, 1952). The type of study made possible by this approach is exemplified by a recent report upon the fate of testosterone administered intravenously to human subjects in health and with hepatic dysfunction (West, Tyler and Samuels, 1951) and during the past year I have been privileged to spend several months with Professor Samuels and his group at the University of Utah and to apply some of the principles which they have evolved to a study of the metabolism of intravenously administered progesterone (Sommerville and Bigler, 1952).

The aim of this work was to develop a micro-method for the determination of progesterone, pregnanediol—in the free form and as the glucuronide—and, if possible, other metabolites of the hormone, in a single sample of peripheral venous blood (30 ml.). Although the experiments are at a very preliminary stage, considerable progess has been made with respect to determination of the metabolite in laked blood before and after hydrolysis by the enzyme β-glucuronidase. Ether-chloroform extracts are purified by chromatography on alumina and, to ensure the maximum degree of specificity, further purification is necessary before application of the relatively non-specific sulphuric acid reaction.

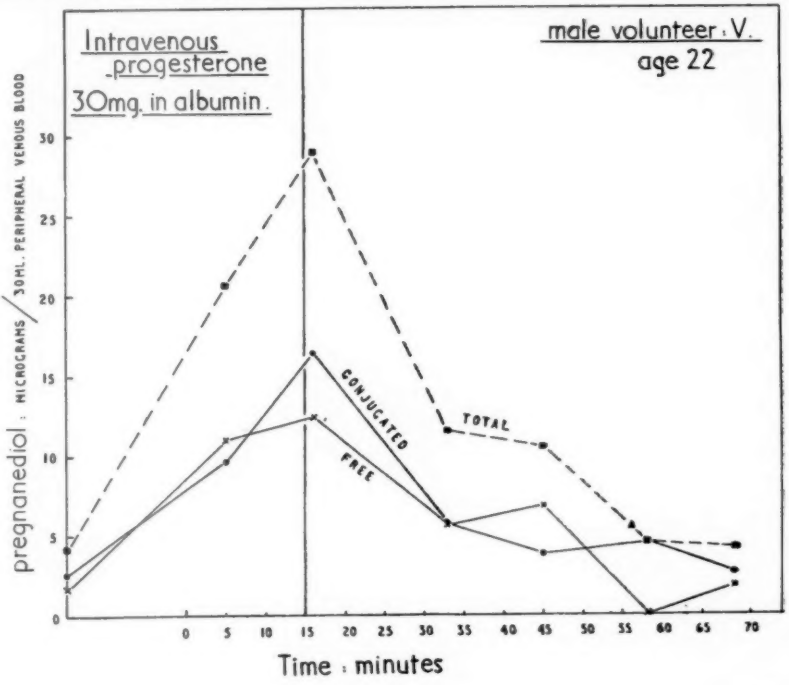

FIG. 1.

Two metabolic experiments are illustrated in Figs. 1 and 2. Fig. 1 shows the levels of circulating metabolite during and after the intravenous infusion of the hormone (in a solution of 25% human serum albumin) to a young man. The level of pregnanediol is expressed in micrograms per blood sample. Fig. 2 shows a similar experiment in a male dog. In this case the determinations were carried out on 20 ml. samples and the result is expressed in micrograms per 100 ml. It will be seen that in both experiments there is evidence of very rapid reduction of the hormone to the metabolite, manifested by the rapid rise in blood level during the infusion. In the human experiment it is especially significant that the level of pregnanediol conjugated as glucuronide is at its maximum at the end-point of the infusion. Following the infusion there is rapid clearance of the steroid from the circulation. Further

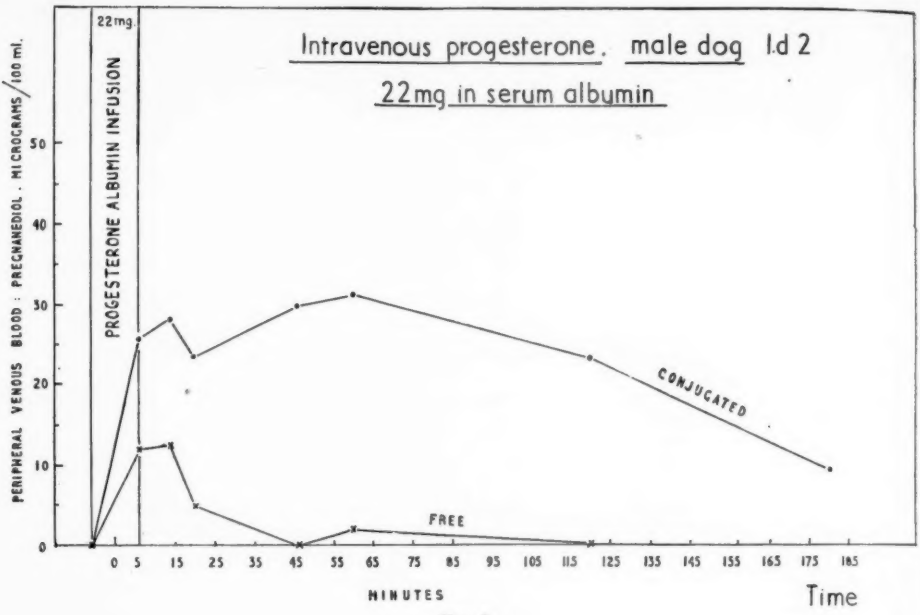

FIG. 2.

experiments must be designed to show to what extent this clearance reflects urinary excretion and to what extent further metabolism of the metabolite.

The micro-method has been applied to the determination of microgram amounts of pregnanediol in urine and the metabolite estimated in hourly samples obtained from human subjects receiving the hormone. The method has also been used for the determination of the steroid in hepatic tissue obtained by laparotomy.

These experiments emphasize our lack of information concerning the mechanism of transport of steroids in the blood stream. Little is known about the factors influencing the dynamic interaction of steroid and protein during transport or about the significance of the conjugation of steroids as glucuronides or sulphates. None the less this recent trend should provide encouragement to the clinical endocrinologist in that it offers the hope of more direct information upon steroid metabolism in human subjects.

New techniques should be applicable to the determination of circulating steroids of endogenous origin and would afford an opportunity for a study of arteriovenous differences in situ. It should be possible to obtain information concerning the renal clearance of metabolites in health and disease and this information will aid the physician in the interpretation of data which have already been obtained by urinalysis.

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